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Genes Controlling Affiliative Behavior as Candidate Genes for Autism

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Abstract

Background—Autism Spectrum Disorders (ASD) are neurodevelopmental disorders of complex etiology, with a recognized substantial contribution of heterogeneous genetic factors; one of the core features of ASD is a lack of affiliative behaviors.

Methods—Based on the existing literature, in this study we examined the hypothesis of allelic associations between genetic variants in six genes involved in control of maternal and affiliative behaviors (*OXT*, *OXTR*, *PRL*, *PRLR*, *DβH*, and *FOSB*). One hundred and seventy-seven probands with ASD from 151 families (n=527) were assessed with a set of related instruments capturing multiple facets of ASD. Multivariate and univariate phenotypes were constructed from these assessments and subjected to genetic linkage and association analyses using PBAT and FBAT software.

Results—The resulting pattern of findings, in general, confirmed the hypotheses of the significance of the genes involved in the development of affiliative behaviors in the manifestation of ASD (P-

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www.ncbi.nlm.nih.gov/

www.people.fas.harvard.edu/~tjhoffm/pbatR.html

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values ranging from 0.000005 to 0.05); statistically speaking, the strongest results were obtained for allelic associations with the *PRL*, *PRLR*, and *OXTR* genes.

Conclusions—Here we provided further evidence of an association between the allelic variants in a number of genes controlling affiliative behaviors and ASD. The outcomes of this study (a) contribute to a number of existing literatures on ASD, (b) allow formulation of new hypotheses of the involvement of the genes studied in this report, and (c) may enhance our understanding of previous reports of associations between ASD and other candidate genes (e.g., serotonergic and GABAergic).

Keywords

Autism Spectrum Disorders; Affiliative behaviors; Allelic association studies; *OXT*; *OXTR*; *PRL*; *PRLR*; *DβH*; *FOSB*

There is convincing evidence that Autism Spectrum Disorders (ASD), a family of disorders characterized by impairments in social, linguistic, and motor functioning, are highly heritable (1). Yet, specific genetic mechanisms underlying this heritability have not yet been discovered. In addition, a substantial number of environmental factors are known, at least in their extremes, to lead to autism-like symptoms (2). Correspondingly, the dominant hypothesis regarding the etiological factors underlying ASD is oligogenic inheritance with possible epistatic interactions among common risk-predisposing genetic variants and detrimental environments (3).

As of today, only about 10% of all ASD cases have been attributed to known etiologies (4,5). Recognition of the complexity of the genetic mechanisms of autism explains why its biology remains elusive and molecular mechanisms underlying this biology mostly speculative or unknown. The field is exploring multiple lines of inquiry, one of which is to investigate a componential nature of the disorder (6) and formulate hypotheses targeting its specific facets (i.e., social, linguistic, and motor impairments). One such hypothesis is aimed at social impairment in ASD and links animal-based investigations of species-typical social behaviors (e.g., affiliative behaviors, pair bonding, social processing) to studies of ASD (7-9). Capitalizing on this line of thinking, we designed a study to test a subset of the genes implicated in aspects of affiliative behavior (7).

Oxytocin (OT) is a neurohypophyseal peptide that has emerged in studies of rodents (7), nonhuman primates (10), and humans (11,12) as an important mediator of affiliative behavior. There are also specific hypotheses (supported by varying degrees of evidence) linking oxytocin and ASD, specifically, that autistic children tend to be characterized by lower levels of plasma OT (13,14), and that infusion of OT is related to the reduction of repetitive behaviors in patients with ASD (15). For example, it has been hypothesized that administration of OT during labor can generate excess OT in the fetal brain. Such excesses might lead to downregulation of OT receptors and, subsequently, to imbalance of the OT system and unavailability of OT for further signal transduction cascades (16). A general dysregulation of the OT system has been conjectured in humans with autism (9). Although there is indirect support from animal studies for this hypothesis (9), experimental studies with humans are difficult to conduct and descriptive studies with humans have produced contradictory results (17-19). Also of note is that maternal OT has been related to switching GABA signaling in the fetal brain during delivery (20). Because GABA signaling is seen as one of the disrupted process in ASD (21), it is possible that oxytocin is indirectly associated with this deficiency. Thus, there is suggestive evidence connecting OT and ASD, but the underlying mechanics of this connection are not known. OT exerts its functions in the brain through OT ligands and receptors and the corresponding genes. Linkage and association studies of ASD have also provided evidence regarding the potential role of oxytocin in the etiology of autism. Specifically, a combined analysis of Autism Genetic Resource Exchange (AGRE) and a sample of Finnish families of probands with autism (22) implicated region 3p24–26, harboring the oxytocin receptor gene,

as a susceptibility region for autism. In this study, the signal was stronger in the Finnish sample. Another whole-genome scan also pointed to this region as the second best locus (23). Association studies with Chinese Han (24) and US Caucasian families (25) of probands with autism implicated the oxytocin receptor gene as a candidate gene for autism (24). Correspondingly, in this study, we considered both the OT (*OXT*, OMIM 167050; GenBank accession NM_000915; chromosome 20p13) and the OT receptor (*OXTR*, OMIM 167055; GenBank accession NM_000916; chromosome 3p26) genes as possible candidate genes for ASD.

Similar to OT, prolactin (PRL) is a pituitary hormonal peptide. PRL has been implemented in parturition, stimulation of mammary gland development during pregnancy, stimulation of milk synthesis, and regulation of lactation, making it an important agent in regulating affiliative behaviors (7). The literature contains some suggestive evidence regarding the role of PRL in the manifestation of autism. Specifically, there are studies reporting an elevation of serum PRL in autism (26), especially in probands with seizures (27), and responsiveness of the PRL system to the administration of m-chlorophenylpiperazine (m-CPP) to adults with autism (28). Similar to studies of OT in autism, the literature is suggestive but not causative and not without complexities. Specifically, 50% of the patients in a study indicating an elevated serum PRL were on neuroleptic treatment, and, although the drugs were stopped for the purposes of the study, an insignificant amount of the medication could have remained in the blood and resulted in an elevated amount of PRL (26). It is also interesting to note that the administration of m-CPP resulted not only in significantly increased PRL response when compared with controls, but also in an increase in repetitive behaviors (28); yet, the nature of the association between increased PRL and increased repetitive behaviors is not clear. In the current study, we investigated both the PRL ligand (*PRL*, OMIM 176760; GenBank accession NM_000948; chromosome 6p22) and the PRL receptor (*PRLR*, OMIM 176761; GenBank accession NM_000949; chromosome 5p13) as ASD candidate genes. Various genome-wide screens point to the regions harboring these genes as of interest [for 6p (29) and for 5p (29-31)], however, neither region maintained significance in a meta-analytic reevaluation (32).

Another biological agent on which the literature on autism and affiliative behavior converge is the enzyme dopamine beta hydroxylase (D β H), involved in the catalyses of dopamine to norepinephrine. D β H is coded by a single gene. There are several animal models in which loss of this gene is strongly associated with deficits in affiliative behaviors [for a review, see (7)]. Studies in humans have reported decreased serum D β H in probands with autism and their parents (33,34). In addition, some evidence suggests that maternal variation in D β H is associated with the manifestation of autism in their children (34,35). The gene coding for the D β H enzyme (*D β H*, OMIM 609312; GenBank accession NM_000787) is located on chromosome 9q, which has been indicated as a region of interest in at least one genome-wide screen for autism (29).

The last candidate gene considered in this study was *FOSB* (OMIM 164772; GenBank accession NM_0006732; chromosome 19q), part of the Fos gene family, whose proteins can form transcription factor complexes. Through their transcription functions, these proteins are involved with proliferation, differentiation, and transformation. The *FOSB* gene has homologs in many species. Mice lacking *fosb* show marked deficits in affiliative behavior, including a failure to retrieve and nurse pups (7). This gene has never been investigated as a candidate gene in autism, although four independent genome-wide scans identified 19q as a region of interest (29,31,36,37).

Methods and Materials

Participants

To test our hypotheses on the relevance of one or more of six genes involved in control of affiliative behaviors (*OXT*, *OXTR*, *PRL*, *PRLR*, *DβH*, and *FOSB*) to ASD, we genotyped DNA from a sample of probands with autism and their families available through the Yale Child Study Center. The sample consisted of 527 participants (322 males and 205 females), of which 177 were classified as probands (see Table 1). These participants formed 151 nuclear families. Forty-one percent of the families had only one child (62), 39% had two children (57), 17% had three children (25), and only five families had four to five children (3 and 2, respectively). Most of the proband children (154, or 87%) were male; the gender distribution among parents or non-proband siblings was about equal. The majority of the sample was Caucasian (93%). Additional relevant characteristics of this sample are shown in Table 1. The study was approved by the Yale IRB.

Phenotyping

Probands and their relatives were evaluated with a number of clinical instruments used for ASD diagnosis [Autism Diagnostic Interview, ADI (38), and Autism Diagnostic Interview–Revised, ADI-R (39); Autism Diagnostic Observational Schedule, ADOS (40) and Autism Diagnostic Observational Schedule–Generic, ADOS-G (41); and Vineland Adaptive Behavior Scales (42)], from which a number of phenotypes were developed. Specifically, the ADI and ADI-R generated five indicators, *Social Interactions*, *Communication*, *Restricted/Repetitive Behaviors*, *Onset*, and *ADI-Based Diagnosis*. The ADOS and ADOS-G also resulted in four quantitative indicators, *Social Skills*, *Communication Skills*, *Stereotyped Behaviors*, and *Imaginative Skills*, and the *ADOS-Based Diagnosis* qualitative variable. The administration of the Vineland resulted in four subscores, *Communication*, *Daily Living Skills*, *Socialization*, *Motor Skills*, and the *Vineland Composite Score*. In addition, *Clinical Diagnosis* (any type of ASD, yes/no) was used in our analyses; this diagnosis relied on judgment of expert clinicians. These 16 univariate phenotypes were clustered into seven partially overlapping multivariate phenotypes, with phenotype 1 capturing convergent diagnostic information; phenotypes 2–4 reflecting specificity of each instrument used in the sample's assessment, and phenotypes 5–7 reflecting the three facets of ASD: (1) *All Diagnoses* (*Clinical Diagnosis*, *ADOS Diagnosis*, and *ADI Diagnosis*); (2) *ADI Group* (all five indicators generated by ADI and ADI-R); (3) *ADOS Group* (all four indicators generated by ADOS and ADOS-G); (4) *Vineland Group* (all indicators except the *Composite Score*, generated by the Vineland Assessment); (5) *Social Skills* (as captured by corresponding indicators from ADI/ADI-R, ADOS/ADOS-G, and the Vineland); (6) *Communication Skills* (as captured by corresponding indicators from ADI/ADI-R, ADOS/ADOS-G, and the Vineland); and (7) *Stereotyped Behaviors* (as reflected by corresponding scales of ADI/ADI-R and ADOS/ADOS-G).

Genotyping

Multiple standard methods were used to extract DNA from blood collected in ACD or buccal cells. The six candidate genes described earlier were captured by 17 SNPs (see Table 2). The SNPs were carefully selected to cover a variety of haplotype blocks in specific genes and to reveal minor allele frequencies not lower than ~10% in Caucasian populations. The SNP alleles were determined by TaqMan SNP Genotyping Assays on the ABI Prism 7900HT and analyzed with SDS software. The probe was obtained from Applied Biosystems (Foster City, CA).

Statistical Analyses

For data cleaning and processing, we used R. We also used PBAT(43), specifically R library *pbatR*, for screening procedures and multivariate tests, and FBAT(44) for univariate and

haplotype tests. We performed the analyses under the null hypotheses of “no association in the presence of linkage” for the recessive model. We selected the recessive model based on the results from previous linkage studies of ASD (45) and the recommendations in the literature (46). Rejecting the null hypothesis of no association suggests an actual allelic association that goes far beyond the weaker conclusion of linkage. The analyses were carried out with the optimal power offset (i.e., a variable offset is found by PBAT for each trait to maximize the power of the PBAT statistics) (47,48). Thus, here we present tests carried out under the null hypothesis of no association on recessive genetic models with a single offset. As mentioned earlier, we also performed PBAT and FBAT tests under the standard but less general null hypothesis of no linkage and no association. The results were consistent with those under the more interesting “no association” hypothesis (complete tables for these analyses available on request). We first present empirical P-values and then discuss the issue of correcting for multiple comparisons.

Results

The patterns of analysis for multivariate and univariate phenotypes are quite consistent. Specifically, for multivariate analyses, the lowest P-values obtained were those for *PRLR* ($P = .000005$, with the multivariate indicator of *Communication Skills* and rs7727306 and $P = .000249$, with the multivariate ADI phenotype, *ADI Group* and rs35614689) and *PRL* ($P = .000085$ and $P = .006957$, with the multivariate ADI phenotype and rs1341239 and rs1205961, respectively). The pattern of univariate results is supportive, highlighting, for associations with the *PRLR* gene, the phenotype *ADOS-Stereotyped Behaviors* ($P = .039409$ for rs35614689) and, for the associations with the *PRL* gene, the *Vineland-Social* ($P = .044005$ for rs1341239) and *ADI-Based Diagnosis* ($P = .025527$ for rs1205961) phenotypes.

Similarly, there is convergent evidence for the association with the *OXTR* and *OXT* genes, both for a variety of multivariate ($P = .007972$ for *Clinical Diagnosis*, $P = .001843$ for *ADI Group*, $P = .018209$ for *Communication Skills* and $P = .006633$ for *Stereotyped Behaviors* with rs2268493 of the *OXTR* gene, and $P = .015761$ for *Stereotyped Behaviors* with rs2740204 of the *OXT* genes, respectively) and univariate (for rs2268493 of *OXTR*, $P = .000978$, .011046, .012727, and .035048, for *ADI-Based Diagnosis*, *ADI-Restricted/Repetitive Behaviors*, *ADOS-Stereotyped Behaviors*, and *Clinical Diagnosis*, respectively; for rs2740204 of the *OXT* gene, $P = .012738$ for *ADOS-Stereotyped Behaviors*) phenotypes.

Finally, there is convergent although not strong evidence from both multivariate and univariate phenotypes regarding associations with autism indicators and the remaining two genes investigated in this study, *DβH* and *FOSB*. The presence of association with the two SNPs of the *DβH* gene is captured by a repetitive set of multivariate P-values (see Table 2) and supported by univariate ones (for rs2519148 with the *Vineland's Communication*, $P = .035981$, *Daily Living Skills*, $P = .004197$, *Socialization*, $P = .006667$, *Motor Skills*, $P = .032184$, and *Composite Score*, $P = .007323$; for rs2073837 with the *ADOS's Stereotyped Behaviors*, $P = .014762$ and *Imaginative Skills*, $P = .018242$ and with the *ADI-Based Diagnosis*, $P = .033303$). Similarly, both sets of phenotypes consistently implicate *FOSB* as associated with ASD. Three of the SNPs in this gene show consistent associations with multiple phenotypes (rs1049739 and rs7256242, both multivariately, see Table 2, and univariately, with *ADOS Stereotyped Behaviors*, $P = .038450$ and *ADI Restricted/Repetitive Behaviors*, $P = .008365$ and $P = .007427$, respectively; and rs2276469, only univariately, with *Clinical Diagnosis*, $P = .014081$, and with *ADI's Communication*, *Restricted/Repetitive Behaviors*, and *ADI-Based Diagnosis*, $P = .029669$, .012449, and .010176, respectively).

Haplotype analyses of the studied genes also provided support for the presence of association. Specifically, the *PRLR* T-T-G haplotype (rs37370, rs249522, rs35614689) appeared to be

overtransmitted (P-values of .0319, .0232, and .0406, for *ADOS-Based Diagnosis* and ADI's *Restricted/Repetitive Behaviors* and *Communication*, respectively). The ADOS's *Stereotyped Behaviors* was associated with the G-G haplotype of the *OXT* gene ($P = .0166$), but no *PRL* or *OXTR* haplotypes were overtransmitted in this sample, as indicated by a lack of association with any of the analyzed phenotypes. The A-G haplotype of the *D β H* gene was associated with the ADI's *Onset* ($P\text{-value} = .0476$) and *ADI-Based Diagnosis* ($P\text{-value} = .0257$) phenotypes. Finally, the SNPs in the *FOSB* gene revealed a consistent association with the phenotypes of *Clinical Diagnosis* and all ADI-based phenotypes. Specifically, all pairwise combinations and combinations of three and four SNPs were statistically significant, with P-values ranging from .0158 to .0051.

Given that the assessment techniques resulted in the creation of 23 phenotypes (7 multivariate and 16 univariate) described earlier and that we used 17 SNPs, we introduced a methodology to correct for multiple testing. To mitigate somewhat the conservative nature of the traditional Bonferroni correction, we used a modified Bonferroni correction. We implemented a two-stage strategy that uses PBAT to estimate powers of phenotype–allele combinations and select the most powerful such combinations, and then uses FBAT to test the selected combinations. The key to the validity of the strategy is that disjointed portions of the data are used in the two stages. Consider the combination of a given subset of phenotypes and a given marker allele. PBAT produces power estimates for that combination by making use of the parental genotypes and children's phenotypes, and ignoring child genotypes that would drive any subsequent FBAT analysis. PBAT estimates genetic effect sizes in a model of the subset of phenotypes, and those effect sizes are then used to estimate power for a hypothetical FBAT analysis of that phenotype–allele combination. The second stage, which uses children's genotypes in an FBAT analysis, is performed only if the power estimated in the first stage is sufficiently high. In our case, we selected the phenotype–allele combinations with estimated power higher than the median of the estimated powers of all such combinations, reducing the number of combinations to be tested by a factor of two. The reduced numbers of combinations were used in the two Bonferroni corrections (one for multivariate and one for univariate phenotypes); the obtained P-value thresholds were 0.00042 for multivariate and 0.00018 for univariate P-values, for overall levels of .05 taking multiple testing into account.

The pattern of results changes after the introduction of such a correction, so that only three multivariate P-values and no univariate ones survive. Specifically, the strongest P-values implicated *PRLR* and *PRL* genes as associated with the multivariate phenotypes *ADI-Group* ($P = .000249$ for *PRLR*'s rs35614689 and $P = .000085$ for *PRL*'s rs1341239) and *Communication Skills* ($P = .000005$ for *PRLR*'s rs7727306). Yet, as indicated earlier, the univariate and haplotype analyses supported the presence of association of ASD with these genes overall rather consistently. Because our analyses extend previously reported findings or hypotheses in the literature, we present here the general pattern of results, but this pattern of results should be interpreted with caution.

Discussion

A number of observations are of interest here.

First, the evidence of the involvement of the prolactin system at the genetic level is novel, although based on evidence in the literature. It is of interest and importance that both the *PRL* ligand and the receptor show allelic associations with ASD. This might suggest the involvement of the *PRL* pathway as a whole and possibly of other pathways with which *PRL* interacts. For example, there is evidence that stimulation by *PRL* of mouse mammary glands results in the expression of genes involved in the biosynthesis of serotonin (e.g., tryptophan hydroxylase

(49)); correspondingly, disruptions of the PRL system might lead to disruption in the serotonin system, something for which there is a great deal of evidence in ASD (50).

Second, by revealing an allelic association between ASD and the oxytocin receptor gene, we have contributed to the growing literature attesting to the presence of this association (24,25). Although none of the previously used SNPs were used here, the SNP found to be associated in both previous studies of *OXTR*, rs2254298, is in the same linkage disequilibrium block as rs2268493, the SNP that showed associations with both multivariate and univariate phenotypes in our study. This finding contributes directly to the growing evidence of the involvement of OT in the formation of affiliative behaviors in general and their disruption in ASD in particular, and indirectly to hypotheses of possible connections between the OT and GABA systems, the latter being consistently implicated in ASD (50).

Third, although no single P-value reached a corrected threshold for any specific SNP/haplotype and phenotype combinations, the presence of allelic associations with both *DβH* and *FOSB*, as indicated by moderate but plentiful P-values, is also of interest. Specifically, there is a consistent pattern of univariate P-values between *DβH* and the Vineland indicators (5 out of 5 comparisons with the Vineland phenotypes produced significant P-values). Similarly, the haplotype analyses of the SNPs in *FOSB* and the ADI-based phenotypes resulted in 60 comparisons with P-values < .05 and 19 comparisons with P-values < .10 out of 105 possible combinations). These observations are further supported by our exploratory analyses of the sample of families in which the probands had a diagnosis of autism proper. In this set of families, *DβH*'s rs2073837 showed P-values of .019979 and .005257 with the multivariate phenotypes of *Communication* and *Social Skills*, respectively. Similarly, *FOSB*'s markers rs1049739 and rs2276469 demonstrated allelic associations with facets of autism (P-values of .000002 and .001075 with *ADOS-Group* and *Communication Skills*, respectively), among other less impressive P-values.

Thus, taken as a whole, these results indicate the association between autism and the group of genes regulating affiliative behaviors (7). None of the studied SNPs tapped functional polymorphisms whose role is studied or known. Correspondingly, at this point, all that can be said is that these results indicate the presence of statistical association between various aspects of the ASD phenotypes and the genes of interest. These associations need to be investigated further for replication and confirmation purposes (51), their translation into the understanding of the underlying biology (52), an appreciation of possible higher order-effects between multiple genetic variants (53), and the role of formative early environmental events (7) in intensifying or diminishing genetic risk.

The final note here is concerned with the observed variability in the results obtained for specific assessment devices and various facets of ASD. Although the results are diverse and, from a certain point of view, not easily interpretable, they contribute to multiple literatures. Specifically, it is interesting that the "featured" assessment for this set of findings is the ADI. In essence, it is no surprise that we observed a lack of convergence in the results for ADI and ADOS, since there is a substantial behavioral literature (54-57) demonstrating the lack of correlation between these two assessments. This pattern of results, encompassing both points of convergence and divergence between ADI and ADOS, needs to be investigated further to be informative and instructive for both researchers and practitioners working with ASD, since both assessments are used as central devices for diagnostic purposes. Similarly, of note is the variability of the results, characterizing different facets of ASD. It appears that different facets of the ASD phenotypes might be associated with specific genes just as specific genes appear to be differentially associated with aspects of affiliative behaviors (7). These findings contribute to an ongoing debate (58) that, on one hand, questions the value of reducing complex multidimensional disorders such as ASD to a single diagnosis, although its degree of inclusivity

can vary, and, on the other hand, brings up issues such as measurement noise and higher rates of Type II error characteristic of componential, facet-based approaches to complex conditions. In addition, our findings, especially those pertaining to associations with $D\beta H$, contribute to the literature on the importance of including the Vineland in studies of etiology of ASD(59).

In sum, these results provide incremental evidence of an association between the allelic variants in a number of genes controlling affiliative behaviors and ASD. As such, they (a) contribute to a number of existing literatures on ASD, (b) allow formulation of new hypotheses of the involvement of the genes studied in this report, and (c) may enhance our understanding of previous reports of associations between ASD and other candidate genes (e.g., serotonergic and GABAergic). However, most importantly, this report contributes to the growing appreciation of the complexity and heterogeneity of the genetic risk factors involved in the manifestation of ASD and its various facets. Careful and detailed phenotypic characterizations, large samples, and thoughtful hypotheses regarding possible underlying biological mechanisms of ASD should all contribute to understanding the etiology of this devastating developmental condition.

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Table 1
Descriptive Statistics on the Sample of Families of the ASD Probands

Total number of people genotyped	472
Male (%)	62.3
Female (%)	37.7
Number of probands per family	
1	129
2	21
3	2
Average age of the probands	10.97
Average Full-Scale IQ of the probands	96.65
Average Vineland Composite Score of the probands	55.38
Probands' Diagnoses	
Autism	84
Asperger's Disorder	46
Pervasive Developmental Disorder-Not Otherwise Specified	40
Childhood Disintegrative Disorder	7

Note: IQ was assessed by a variety of means, including the WISC, WPPSI, the DAS, the Mullen, the K-ABC, and the Leiter Test of Intelligence (Leiter-R), depending on the proband's age and level of functioning and the availability of particular versions of these tests at a given time of testing

Table 2

Results of Multivariate Analyses with PBAT under Recessive Model

Phenotypes	All Diagnoses	ADI Group	ADOS Group	Vineland Group	Social Skills	Communication Skills	Stereotyped Behaviors
Polymorphisms							
<i>OXTR</i> rs2770378							.015761
<i>OXTR</i> rs2740204							
<i>OXTR</i> rs237885							
<i>OXTR</i> rs2268493	.007972	.001843				.018209	.006633
<i>OXTR</i> rs237898							
<i>PRL</i> rs1205961		.006957					
<i>PRL</i> rs1341239		.000085					
<i>PRLR</i> rs37370							
<i>PRLR</i> rs249522							
<i>PRLR</i> rs35614689		.000249				.000005	
<i>PRLR</i> rs7727306							
<i>DBH</i> rs2519148				.026973	.016459		
<i>DBH</i> rs2073837			.047908	.037380		.018443	.053895
<i>FOSB</i> rs2276469							
<i>FOSB</i> rs1049739			.013351				.017601
<i>FOSB</i> rs7256242	.037964						
<i>FOSB</i> rs12972892							

Note: Only statistically significant values (at $P < .05$) are presented; italicized values indicate P-values surviving correction for multiple comparison.