RESEARCH ARTICLE

AMERICAN JOURNAL OF medical genetics PART B
Neuropsychiatric Genetics

# An Association and Haplotype Analysis of Porcine Maternal Infanticide: A Model for Human Puerperal Psychosis?

**C.R. Quilter,[1]* C.A. Sargent,[1] J. Bauer,[1] M. R. Bagga,[1] C. P. Reiter,[1] E. L. Hutchinson,[2] O. I. Southwood,[3] G. Evans,[3] A. Mileham,[3] D.K. Griffin,[2] and N.A. Affara[1]**

[1]Human Molecular Genetics Group, Department of Pathology, University of Cambridge, Cambridge, UK

[2]School of Biosciences, University of Kent, Canterbury, Kent, UK

[3]PIC, Genus plc (PIC), Nantwich, UK

Manuscript Received: 13 March 2012; Manuscript Accepted: 9 August 2012

**An association analysis using the Illumina porcine SNP60 beadchip was performed to identify SNPs significantly associated with porcine maternal infanticide. We previously hypothesised that this was a good animal model for human puerperal psychosis, an extreme form of postnatal mood disorder. Animals were selected from carefully phenotyped unrelated infanticide and control groups (representing extremes of the phenotypic spectrum), from four different lines. Permutation and sliding window analyses and an analysis to see which haplotypes were in linkage disequilibrium (LD) were compared to identify concordant regions. Across all analyses, intervals on SSCs 1, 3, 4, 10, and 13 were constant, contained genes associated with psychiatric or neurological disorders and were significant in multiple lines. The strongest (near GWS) consistent candidate region across all analyses and all breeds was the one located on SSC3 with one peak at 23.4 Mb, syntenic to a candidate region for bipolar disorder and another at 31.9 Mb, syntenic to a candidate region for human puerperal psychosis (16p13). From the haplotype/LD analysis, two regions reached genome wide significance (GWS): the first on SSC4 (*KHDRBS3* to *FAM135B*), which was significant (−logP 5.57) in one Duroc based breed and is syntenic to a region in humans associated with cognition and neurotism; the second on SSC15, which was significant (−log10P 5.68) in two breeds and contained *PAX3*, which is expressed in the brain.**

© 2012 Wiley Periodicals, Inc.

**Key words:** SNP; animal model; postnatal mood

**How to Cite this Article:**
Quilter CR, Sargent CA, Bauer J, Bagga M, Reiter C, Hutchinson E, Southwood O, Evans G, Mileham A, Griffin DK, Affara NA. 2012. An Association and Haplotype Analysis of Porcine Maternal Infanticide: A Model for Human Puerperal Psychosis?
Am J Med Genet Part B 159B:908–927.

## INTRODUCTION

Porcine infanticide is defined in this study as pigs who attack and kill their newborn offspring within 24 hr of birth, by biting them to death [Knap and Merks, 1987; Van der Steen et al., 1988]. This is in contrast to normal porcine behaviour after giving birth, which is characterized by passivity, general unresponsiveness to piglets and lateral lying to allow maximum access to teats [Jarvis et al., 1999]. Large surveys of commercial pig farms looking at maternal infanticide in gilts (primiparous) have reported the incidence to vary between 0.6% and 12% [Knap and Merks, 1987; Van der Steen et al., 1988; Harris and Gonyou, 2003]. Some studies have also included sows; Chen et al. [2008] observed that infanticide was present in 12.8% of gilts, which reduced to 7.5% and 4.5% in their 2nd and 3rd parities respectively.

There are several factors, which may contribute to porcine infanticide, including farm environment [Jarvis et al., 1999, 2004; Ahlström et al., 2002], previous maternal experience [Van der Steen et al., 1988; Chen et al., 2008] and a strong heritable component [Knap and Merks, 1987; Van der Steen et al., 1988]. Therefore, a genetic predisposition to aggressive infanticide clearly exists, which is ameliorated by experience but may also be influenced by the environment. Chen et al. [2008] observed that sows prone to infanticide may be more restless before giving birth compared to those who are not at risk but in general it is difficult

Additional supporting information may be found in the online version of this article.

The authors have no conflict of interest to declare.

Grant sponsor: Department for Environment, Food and Rural Affairs (DEFRA).

*Correspondence to:
C.R. Quilter, E-mail: crq20@cam.ac.uk

Article first published online in Wiley Online Library (wileyonlinelibrary.com): 13 September 2012
DOI 10.1002/ajmg.b.32097

to predict which animals are likely to exhibit this undesirable behavior.

Puerperal psychosis is a severe form of post-natal mood disorders, which includes symptoms of mania and depression and psychotic symptoms such as delusions and hallucinations. It is related to, and may even be a subset of, bipolar disorder (BP; manic depression) [Jones and Craddock, 2002]. A recent linkage study investigating bipolar affective puerperal psychosis in humans found genome wide significant linkage on 16p13 and genome wide suggestive linkage on 8q24 [Jones et al., 2007]. In addition, Mahon et al. [2009] fine mapped their best regions from an initial linkage study in humans and found single nucleotide polymorphisms (SNPs) associated with increased susceptibility to postpartum mood symptoms on chromosomes 1q21.1-q32.1 and 9p24.3p22.3.

On the basis of previous mapping and gene expression studies we have proposed that porcine maternal infanticide may be a good animal model for human postnatal illness, and mood disorders [Quilter et al., 2007, 2008]. Our affected sib pair whole genome linkage analysis, identified 4 QTL mapping on *Sus scrofa* chromosomes 2 (SSC2), 10 (SSC10) and two on the X (SSCX). Two regions on SSC1 were noted but not reported because they did not quite reach significance (Quilter, unpublished). A larger study by Chen et al. [2009] on a Chinese F2 resource population also identified QTL on SSC2 and SSCX, in addition to QTL on SSC6, SSC14 and SSC15. In a parallel microarray study of gene expression in hypothalamus samples from nine matched pairs of infanticide versus control animals, we identified 129 differentially expressed genes, some of which were common to our microsatellite screen [Quilter et al., 2008].

The aim of this current study was to confirm and refine QTL identified by our previous work and studies reported by others [Chen et al., 2009], with the intention of providing further data to support the hypothesis that this behavior in pigs is a good animal model for postnatal mood disorders in humans. An association study was carried out using the Illumina Porcine SNP60 BeadChip (http://www.illumina.com/pages.ilmn?ID=320). This chip contains >60,000 single nucleotide polymorphisms (SNPs), providing markers at an estimate of one marker per 40 kb across the pig genome (see Ramos et al. [2009], allowing many extensive studies to be carried out in the pig. Our samples were collected from unrelated populations of infanticide and control animals (representing extremes of the phenotypic spectrum) for four commercially important breeds. The greater resolution of this array not only allowed us to assess our previous work and that of others but also identified new candidate regions and genes that may contribute to the phenotype, in particular chromosome intervals syntenic with regions of the human genome showing significant association with BP and puerperal psychosis.

## MATERIALS AND METHODS

### Animals

The Pig Improvement Company (PIC), which is part of Genus provided the animals used in this study. Animals with maternal infanticide were classified as mothers, that killed at least one of their offspring by biting them to death, within 24 hr of birth. Animals were selected from four different lines (B, C, D, H), which were the same lines with the largest number of sib pairs, used in our previous study [Quilter et al., 2007] (Table I). (A line is a closed commercial breeding population, which may be derived from a single pure breed or crosses between breeds: a breed is a closed pure breeding population which is historically derived from a particular geographic region and which has distinct phenotypic features). For each line, samples were collected from unrelated individuals of carefully phenotyped infanticide and control animals (representing extremes of the phenotypic spectrum).

Even though our animals were selected from closed lines, from unrelated populations, there is still likely to be more genetic relatedness between animals than in human cohorts. Therefore, as the background will have less genetic variation in our animals, any mutation detected is more likely to have a phenotypic association. Significant results can therefore be obtained with fewer animals than the numbers required for human studies.

Pigs were housed in farrowing crates under the same conditions to our previous QTL study (small pens 1.5–2.5 m in length depending on weight of pig, where sows are restricted by bars to prevent crushing of piglets) and were obtained from three different farms. The incidence of aggression for each line was line B 4.8%; line C 5.9%; line D 10.8%; line H 10.3% (2008–2010).

### Genotyping

***DNA isolation.*** Genomic DNA was provided by PIC and extracted from porcine ear and tail tissue using commercial kits (Qiagen, Crawley, UK). DNA was quantified by PIC using picogreen [Ahn et al., 1996].

**TABLE I. The Genetic Background of Each Line, Corresponding Line Reference in Quilter et al. [2007] and Numbers Collected for This Study, Before and After QC**

| Sowline | Total numbers infanticide | Total numbers controls | Infanticide passed QC | Controls passed QC | Breed | Quilter et al. [2007] |
|---|---|---|---|---|---|---|
| B | 57 | 55 | 53 | 51 | Landrace (LR) | B |
| C | 45 | 45 | 44 | 43 | Large White (LW) | C |
| D | 53 | 52 | 51 | 50 | Duroc × LR | D |
| H | 70 | 70 | 69 | 66 | Duroc × LW | H |

***Porcine SNP60 BeadChip.*** Samples were hybridized to the Illumina Porcine SNP60 BeadChip according to the manufacturer's instructions using the Infinium HD assay Ultra protocol (http://www.illumina.com). The BeadChips were scanned using an iScan (Illumina) and an AutoLoader2 (Illumina). The BeadStudio v.3 software (Illumina Corp.) was used for calculating call- and conflict-rates. The SNP sequences were run through BLAST (http://www.ncbi.nlm.nih.gov/BLAST/) in order to match to genes and/or the SNP position as entered into the pig ensemble database (http://www.ensembl.org/index.html), to see which genes were present at that location. Where no genes were present in the pig, the syntenic human region was compared. To date this has been in accordance with ensemble (http://www.ensembl.org/index.html), which uses the pig genome assembly version 9 (Sscrofa9) and verified with NCBI (Sscrofa 10) confirming that markers are in the same order. Gene ontologies were determined using The National Centre for Biotechnology Information (NCBI; http://www.ncbi.nlm.nih.gov/) and The Database for Annotation, Visualization and Integrated Discovery (DAVID) v6.7 (http://david.abcc.ncifcrf.gov/).

## Statistical Analysis

All data sets were analysed by PLINK (http://pngu.mgh.harvard.edu/~purcell/plink/). PLINK is a free, open-source whole genome association analysis toolset, designed to perform a range of basic, large-scale analyses in a computationally efficient manner. An in house pipeline was developed to prepare data from the array for use in PLINK. A quality control (QC) was performed on all the chips and removed any SNPs which failed to be called on >95% of the samples, it also removed any samples that failed to give interpretable results for >95% of SNPs. Criteria thresholds used for filtering (QC):

- max per sample missing: 0.04 (call rate)
- max per genotype missing: 0.04 (SNP call rate)
- minor allele frequency (MAF): 0.01
- Hardy Weinberg equilibrium: $P > 0.00001$

Illumina Porcine SNP60 BeadChip genotyping was obtained for 427 animals after QC. Of the SNPs with a MAF > 0.01, ~50 K SNPs were retained for analysis. An association analysis was carried out for each line, on our population of unrelated samples (Table I) and from lines D and H additional samples representing sib pairs (Dsp 48 pairs, Hsp 31 pairs) were also selected for a sib-pair analysis. SNPs at a 5% confidence level were considered significant and after applying the Bonferroni correction for multiple testing (0.05/50 K), a threshold $P$ value$\leq 1 \times 10^{-6}$ ($-\log10P > 6$) was used to identify associations unlikely to have occurred by chance. This approach was used to identify significant individual SNPs associated with maternal infanticide. A Bonferroni correction should provide more stringent criteria than other correction methods. In addition, a sliding window association analysis was also carried out on our sample population. This examined windows of three consecutive SNPs across the length of the array, that is, this approach looked for the significance of groups of SNPs associated with maternal infanticide. It was carried out separately for each line as combining lines may have led to a population stratification problem.

Two types of permutation analyses to test different models of the data and determine the most robust association intervals were run: (1) an adaptive permutation approach identifies SNPs that are clearly going to be non-significant more quickly than SNPs that look interesting. This was performed to see which SNPs survived $1 \times 10^6$ permutations; (2) in contrast the max(T) permutation does not drop SNPs along the way. Adjustment of $P$ value based on 5,000 permutations was specified, which meant all 5,000 were performed, for all SNPs. As the permutations performed allow control of the family wise error, SNPs with an adjusted $P$ value $<0.05$ were considered to be significant.

Haplotypes were also generated in PLINK using the haploview algorithm and were tested for haplotype case/control associations to see which haplotype blocks were in linkage disequilibrium. A chi-square ($\chi^2$) statistic was used to test for association and our cut off was a $\chi^2$ value >14.4 (1 df) that gave a probability ($P$) of $P < 0.0001$ (using a chi-square to $P$ calculator (http://faculty.vassar.edu/lowry/tabs.html#csq); for 1 degree of freedom (df) NB omnibus intervals have >1 df so $\chi^2$ is higher). These top regions also corresponded to a $-\log10P > 3.85$ from the haplotypic data. The number of haplotypes varied for each line. For each haplotype, the number of SNPs involved for each line were: line B (14,914) C (17,284) D (18,618) H (18,740) and after a correction for multiple testing $-\log10$Ps of 5.47 (B), 5.53 (C), 5.57 (D) and 5.57 (H; average 5.54) were considered to be of GWS.

# RESULTS

## Single SNP Association and Sib-Pair Analysis

Association analysis of unrelated animals and the sib-pair analysis using PLINK were combined to look for significant SNPs or runs of SNPs associated with porcine maternal infanticide. The top $-\log10$ $P$ value for association with a single SNP, after Bonferroni correction, was 5.52 on SSC3 (Fig. 1), which meant that no single SNP reached GWS ($-\log10P > 6$) from this analysis, however several

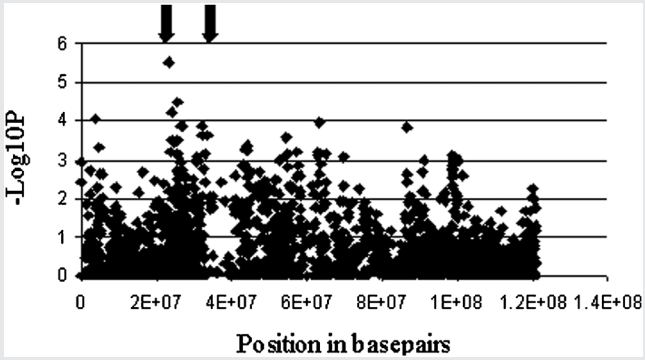


**FIG. 1. The graph shows a summary of the $-\log10P$ values for SSC3, line D for the single SNP association analysis. The first arrow points to the highest peak and represents *GPR139* and the second arrow points to the nearby *RBFOX1* peak.**

top gene regions survived one million permutations (adaptive) and/or were present in all four lines. The most significant regions are summarized in Table II using the following criteria: peak SNPs with a top −log10emp value of >4, survived one million permutations (adaptive) and where all four lines had SNPs ($P < 0.01$) in the candidate region. In order of highest −log10emp these were identified as being present on chromosomes: 3, 8, 4a, 13b, 4b, 6, 13a, 1, and 2. These are new potential candidate regions and the interval on SSC3 is syntentic in humans to 16p, which is indicated in human puerperal psychosis (PP) and bipolar studies (BP) [Jones et al., 2007]. Significantly differentially expressed genes from our previous array analysis of hypothalamic mRNA from infanticidal and non-infanticidal sows [Quilter et al., 2008] were also present in some of these regions: 1q (*C9orf16*, *MED27*), 2 (*MATR3*), 6 (*OSBPL9*), 13a (*STTBB*, *WDR48*) and 13b (*POU1F1*) with *STT3B* and *POU1F1* also being genes with good −log10emp values.

Additional potential candidate regions were highlighted where the peak SNPs had a top −log10emp > 4 and also survived one million permutations (but were not present in all four lines): 2 [Chen et al., 2009], 5a, 9a, 9b, 10a [Quilter et al., 2007], 10b [Quilter et al., 2007], 12a, 12b, 14, 15, 15b, 17, 18. In addition, some regions had peak SNPs with a top −log10emp > 4 and had SNPs ($P < 0.01$) in all four lines in these regions but did not survive one million permutations: in SSC1q (Quilter, unpublished), 5b, 11, X [Quilter et al., 2007; Chen et al., 2009] (supplementary Table I).

## Permutation Analysis

***Adaptive permutation.*** SNPs that survived one million permutations have been considered with the association analysis above (Table II). A complete list of genes that survived one million permutations is summarized in supplementary Table II.

***Max(T) permutation.*** From the max(T) permutation analysis, SNPs with an adjusted *P* value <0.05 were considered to be of genome wide significance. However, our SNPs failed to reach this significance level. The most significant gene regions represented *GPR139* to *IQCK* (SSC3 BP Dick et al. [2002]) with an adjusted p value 0.07518 and 3 SNPs representing 3′*PAX3* (15c) all with adjusted p values of 0.07978. The other top regions were comparable to our other analyses highlighting SNPs in 1q), 4a, 4b, 12a, 12c, 13b, 14, 15a, and 18a with adjusted *P* values <0.4, SNPs from other top regions including 1p (Quilter, unpublished) 3 (PP Jones et al., 2007), 13a, 15 [Chen et al., 2009], 15b, 18b) were found with adjusted p values below 0.8 and regions including 2 [Chen et al., 2009], 14 [Chen et al., 2009], Xp and Xq [Quilter et al., 2007; Chen et al., 2009] with adjusted *P* values below 1. Table III shows data with *P* values ≤0.4, those ≤0.1 are in bold.

## Haplotype Analysis

***Sliding window approach.*** The sliding window association analysis was carried out on our samples and used to rationalize the initial association results and highlight potential causative haplotypes. The majority of haplotypes with a *P* value <0.005 were in regions previously detected by the association analysis, strengthening our initial results. When looking at regions which had consecutive significant haplotypes with at least one haplotype having a *P* value <0.0001, gene regions were confirmed from the association and sib pair analysis and previous QTL analyses on 1p, 1q, 3, 4, 6, and 13 by individual line analysis $P < 0.0001$ (Table IV) and on 1p, 1q, 4, 10, and 13 when regions in common to more than one line were examined at $P < 0.001$ (Table V). The sliding window association analysis also identified potential causative haplotypes. Those that were higher in the aggressive animals are highlighted in gray in Tables IV and V, some of which fall in good candidate regions and most of which fall in previously identified QTL/candidate regions (1q, 3 [BP Dick et al., 2002; PP Jones et al., 2007], 13b).

***Haplotype blocks and linkage disequilibrium.*** A further analysis was run to see which haplotype blocks were in linkage disequilibrium with the aim of rationalizing our initial results and of finding regions of GWS. Top regions were those with a $\chi^2$ value >14.4 (1 df) (equivalent to a *P* value < 0.0001) which corresponded to −log10P > 3.85 from the haplotypic data (Table VI, Fig. 2). Two haplotype blocks reached GWS (∼−log10P 5.54): *KHDRBS3* to *FAM135B* on SSC4 −log10P 5.5707 (line D; confirming region 4a from the single SNP analysis) and 3′*PAX3*, −log10P 5.6844 (line C) on SSC15, (a region present in lines C, D and H ($P < 0.01$) from the single SNP analysis with a top −log10emp 4.1759 and survival of 579,794 permutations). Other gene regions were near GWS and were comparable to candidate regions highlighted by the association analysis or previous analyses: 1q [Quilter et al., 2007], 3 (BP Dick et al., 2002; PP Jones et al., 2007), 4b, 6 [Chen et al., 2009], 12a, 12b, 13b, 14, 15 [Chen et al., 2009], 15b and 18a. The only haplotypic blocks with a $P < 0.0001$ found across all four lines were for the gene region *CLEC19A* to *XYLT1* (SSC3) at 24.1 Mb (BP Dick et al., 2002) with a −log10P 4.494, 5' *RBFOX1* (SSC3) at 32 Mb (PP Jones et al., 2007) with a −log10P 4.107 and *PLEKHG1* (SSC1p) at 16.3 Mb with a −log10P 3.96 (Fig. 1). Supplementary Table III summarizes the gene functions from these top regions and shows that many significant genes are associated with psychiatric and/or neurological disorders. Some information was obtained from Database of Genotypes and Phenotypes (dbGaP), Bethesda (MD): National Center for Biotechnology Information, National Library of Medicine. Available from: http://www.ncbi.nlm.nih.gov/sites/entrez?db=gap [Mailman et al., 2007].

***Confirmation of QTL/gene regions associated with porcine maternal infanticide.*** In order to verify the association and haplotype analysis we looked specifically at the significance of our previous QTL [Quilter et al., 2007] and the QTL/gene regions identified by other studies [Chen et al., 2009], in the context of this analysis (summarized in supplementary Table IV).

Our previous QTL regions [Quilter et al., 2007] were confirmed by the single SNP association analysis on 1q (Quilter, unpublished) and Xp (*MAOA*) which were present in all 4 lines and had top gene/s with a −log10emp > 4 and regions on 10 with top gene/s having a −log10emp > 4 and which survived one million permutations. The chromosomal region on 1p (Quilter, unpublished) was present in all four lines and survived 225,774 permutations. Regions on 1p, 1q, 10 (*PDSS1*) were confirmed by both the max(T) permutation analysis and the haplotypic data, with *SYNE1* and *ESR1* (1p), *MAP3K7* to *MMS22L* (1q) and *NR5A2* and *ZNF281* (10) being highlighted. A region on Xp (*SCML2* to *CDK15*) and a region on Xq (*GPC3*) had a $P < 1$ from the max (T) permutation analysis. The

**TABLE II. Top Regions Identified by Single SNP Association (and Adaptive Permutation) Analysis (CHR Chromosome)**

| CHR | Analyses | 4 lines | Top log10 emp > 4 | 1 million permutations | Common SNPs | Array | Range | Range | Peak | Top genes (peak in bold) |
|---|---|---|---|---|---|---|---|---|---|---|
| 3 | B,C,D,H,Dsp | **Yes** | **5.52287875** | **Yes** | MARC0007734<br>MARC0004212 | No | 18757986 | 34682032 | 23436727 | ***GPR139 to IQCK***<br>*SYT17 to XYLT1*<br>*XYLT1*<br>*XYLT1 to ABCC1*<br>*ABCC1*<br>*MKL2*<br>*ERCC4 to SNX29*<br>*RBFOX1 (A2BP1) to UBN1* |
| 8 | B,C,D,H,Dsp,Hsp | **Yes** | **5.5** | **Yes** | ALGA0105643<br>ASGA0097249 | No | 106761887 | 119613384 | 109926432 | ***GRID2 to FAM190A***<br>*FAM190A*<br>*WDFY3*<br>*CDS1 to NKX6-1*<br>*NKX6-1*<br>*NKX6-1 to AGPAT9*<br>*ENOPH1*<br>*GRID2*<br>*NEAR GRID2* |
| 4a | B,C,D,H,Dsp | **Yes** | **4.92081875** | **Yes** | ALGA0022406 | No | 1008941 | 5407041 | 4170121 | ***FAM135B to KHDRBS3***<br>*Near DENND3*<br>*KHDRBS3 to ZFAT*<br>KHDRBS3 |
| 13b | B,C,D,H,Dsp,Hsp | **Yes** | **4.92081875** | **Yes** | ***BLOCKS LARGE & SMALL***<br>*ALGA0072320, ALGA0072608, DRGA0012994, ASGA0059251, H3GA0037561, MARC0024545, H3GA0037568, ALGA0072642, MARC0026669, ALGA0124066, ASGA0059266, H3GA0037597, ALGA0072725, MARC0082955, ASGA0059288, DRGA0013062, INRA0041230, ALGA0072761, DRGA0013071, DRGA0013076, DRGA0013078, ALGA0072797, DRGA0017463, DRGA0013090, ASGA0059304, CAHM0000041, DRGA0013095, DRGA0013099, M1GA0017722, DRGA0013105, ALGA0118416, DRGA0013113, ALGA0108757, ALGA0073046, ALGA0073051, H3GA0037747, ALGA0073365, ALGA0073655, ASGA0059833, ALGA0073695* | **POU1F1** | 108663622 | 145133007 | 145133007 | ***POFUT2 to ADARB1***<br>*PRSS7* |

(*Continued*)

TABLE II. (*Continued*)

| CHR | Analyses | 4 lines | Top log10 emp > 4 | 1 million permutations | Common SNPs | Array | Range | Range | Peak | Top genes (peak in bold) |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | *GBE1 to ROBO1* |
| | | | | | | | | | | *ROBO1 to LIPI* |
| | | | | | | | | | | *nr SYNJ1, C21ORF62* |
| 4b | B,C,D,Dsp,Hsp | **Yes** | **4.82390874** | **Yes** | ***BLOCK*** | No | 113085778 | 116902813 | 115510651 | ***WDR47*** |
| | | | | | **M1GA0006444** | | | | | ***CLCC1*** |
| | | | | | H3GA0014224 | | | | | *CLCC1 to AKNAD1* |
| | | | | | ALGA0028142 | | | | | *KCNA3 to PROK1* |
| | | | | | ASGA0022124 | | | | | *SLC6A17* |
| | | | | | MARC0070819 | | | | | *Near TMEM167B* |
| | | | | | INRA0016711 | | | | | *TAF13 to WDR47* |
| | | | | | | | | | | *KIAA1324* |
| 6 | B,C,D,H,Dsp | **Yes** | **4.74472749** | **Yes** | ASGA0091812 | OSBPL9 | 102267809 | 118864291 | 108179295 | ***FGGY*** |
| | | | | | | | | | | *Near FOXE3* |
| | | | | | | | | | | *TESK2* |
| | | | | | | | | | | *SGIP1* |
| 13a | B,C,D,H,Dsp,Hsp | **Yes** | **4.67778071** | **Yes** | ALGA0068765 | **STT3B,** WDR48 | 9445122 | 24299279 | 15356130 | ***Near STT3B*** |
| | | | | | | | | | | *Near ARPP-21* |
| 1 | B,C,D,H,Dsp,Hsp | **Yes** | **4.64878473** | **Yes** | ALGA0008664 | C9orf16, MED27 | 241532914 | 293743936 | 289600000 | ***COL5A1 to PAEP*** |
| | | | | | | | | | | *Near KLF4* |
| | | | | | | | | | | *DBH* |
| | | | | | | | | | | *RXRA* |
| | | | | | | | | | | *FAM75D4 to C9ORF144* |
| 2 | B,C,D,H, Dsp | **Yes** | **4.59555707** | **Yes** | MARC0038009 | MATR3 | 117275412 | 135099064 | 122981778 | ***KIF3A to SEPT8*** |
| | | | | | MARC0035023 | | | | | *IN ARHGAP26* |
| | | | | | H3GA0055612 | | | | | *NR3C1 to HMHB1* |
| | | | | | MARC0055611 | | | | | *KCTD16 to GRXCR2* |

**TABLE III. Top Max(T) Permutation Results**

| LINE | CHR | SNP | EMP1 | EMP2 | Bp | Gene region |
|---|---|---|---|---|---|---|
| D | 1 | ASGA0003159 | 0.0002 | 0.3491 | 63398602 | *MAP3K7 to EPHA7* |
| D | 3 | H3GA0053147 | 0.0002 | **0.07518** | 23436727 | *GPR139 to IQCK* |
| D | 3 | ALGA0113238 | 0.0006 | 0.4 | 24107618 | *CLEC19A to XYLT1* |
| D | 3 | ALGA0124389 | 0.0004 | 0.3805 | 25000000 | *XYLT1 to ABCC1* |
| D | 12 | MARC0069888 | 0.0002 | 0.2056 | 30900000 | *NOG to C17ORF67* |
| D | 12 | H3GA0052480 | 0.0002 | 0.3491 | 31605876 | *MSI2 to MRPS23* |
| D | 12 | MARC0021670 | 0.0002 | 0.1056 | 33550000 | *GDPD1* |
| D | 12 | ALGA0107852 | 0.0002 | 0.1988 | 56072709 | *ZNF624, ZNF287* |
| D | 13 | MARC0043234 | 0.0002 | 0.3971 | 145133007 | *POFUT2 to ADARB1* |
| C | 15 | H3GA0045081 | 0.0002 | 0.1376 | 115578890 | *3′ to PAX3* |
| C | 15 | ASGA0070769 | 0.0002 | **0.07978** | 115603664 | *3′ to PAX3* |
| C | 15 | M1GA0020474 | 0.0002 | **0.07978** | 115636450 | *3′ to PAX3* |
| C | 15 | ASGA0070779 | 0.0002 | **0.07978** | 115655024 | *3′ to PAX3* |
| D | 18 | MARC0112314 | 0.0002 | 0.2132 | 16821623 | *KLHDC10* |

EMP1 is the empirical *P* value before correction and EMP2 is the adjusted empirical *P* value after permutation testing.

QTL on 2 was not confirmed by these analyses but the single SNP criteria showed SNPs in this region with an association significance of $P < 0.01$, found mainly in the sib pair analyses (top SNP: −log 10emp 2.6, 14,445 permutations). In our previous paper, this QTL was line specific to the Large White breed.

To confirm the other porcine analysis [Chen et al., 2009], single SNP association analysis confirmed regions on 2 and 6 as having top gene/s with a $-\log10\text{emp} > 4$ and which survived one million permutations. The region on 15 survived 135,456 permutations (adaptive) and had a p value 0.5437 from the max(T) permutation analysis. Regions on 6 and 15 were also confirmed by the haplotype/LD data ($-\log10P > 3.85$). However, the QTL on SSC14 was not confirmed.

***Top regions.*** A summary of all the analyses described is found in Table VII. From this table, it is clear that the candidate regions on chromosomes 1p (Quilter, unpublished), 1q (Quilter, unpublished), 3 [Dick et al., 2002; Jones et al., 2007], 4a (new), 4b (new) 10 [Quilter et al., 2007] 13a (new) and 13b (new) are common to most analyses ($\geq$4). The region on SSC15 is also deemed important as it reached genome wide significance. Results showed that many significant genes are associated with psychiatric and/or neurological disorders (NCBI, DAVID).

## DISCUSSION

In this study, we initially carried out a single SNP association analysis and although we identified strong candidate regions, we failed to identify any at GWS. Analyzing our results with other statistical methods allowed us to highlight genetic regions, which were concordant. For example, the strongest candidate intervals proposed from the single SNP association also contained genes, which survived a million permutations (adaptive). Results with the best *P* values from the max(T) permutation testing, fell in previously identified regions. The sliding widow haplotype analysis, which looked at blocks of 3 SNPs, confirmed some of the candidate intervals detected by single SNPs. Many genes from the haplotype LD analysis showed strong SNP data, identifying regions of near significance at the chromosome wide level. In fact, by looking at haplotypes in LD, ancestral regions of the pig genome were targeted and therefore considered more likely to contain mutations relevant to the phenotype. Most of these regions were common to the initial single SNP association analysis. This method was also able to identify two intervals at GWS.

In general, regions that were not concordant throughout multiple analyses were considered to be of less significance and/or more likely to be false positives. However, some single significant SNPs from the association analysis were not noteworthy in the haplotype LD analysis because they were not in LD with adjacent SNPs, for example, the most significant SNP in the single SNP association analysis (H3GA0053147), which represented the interval *GPR139* to *IQCK*. For such SNPs, where the initial association data was strong, the gene(s)/genetic region that they represent should still be judged a potential candidate(s).

Therefore by considering multiple analyses, we were able to determine which regions of the porcine genome were the strongest candidates for porcine maternal infanticide and worthy of further investigation. When taking into consideration all analyses, new candidate regions were identified on SSCs 3, 4, 13, and 15 and regions were confirmed on SSCs 1p, 1q (Quilter, unpublished), 10, X [Quilter et al., 2007] and on SSCs 2, 6, and 15 [Chen et al., 2009]. Multiple candidate intervals were therefore detected, which is justified because the genetic contribution to behavioral studies is often complex, involving multiple regions of the genome, some of which may only contribute a small genetic effect. Two intervals (SSCs 4 and 15) reached GWS from our multiple analyses. We postulate that the regions which fall just below GWS from both the association and haplotype analyses, are still of interest and worthy of further investigation, particularly if they are concordant across analyses and are present in multiple lines. This is supported by the fact that genes associated with psychiatric and/or neurodegenerative disorders were found in all of these intervals.

**TABLE IV. Summary of the Results From the Sliding Window Analysis for Each Line, Showing Regions That Contain At Least One Haplotype With a *P* Value <0.0001**

| Line | Chr | Bp | Gene | F_A | Comment |
|---|---|---|---|---|---|
| B | 1 | 14874473 | *SYNE1* | None | QTL 1p Quilter et al. [unpublished] |
| B | 4 | 115416539 | *KIAA1324, C1orf94, TAF13* | None | BLOCK |
| B | 4 | 115468034 | *TMEM167B* | | |
| B | 5 | 63262812 | *IQSEC3* | None | |
| | 5 | 63275184 | *WASH1 RELATED* | | |
| B | 13 | 126311472 | *GBE1 to ROBO1* | None | |
| B | 15 | 29986085 | *EPB41L5* | Lower in A | |
| | 15 | 30518990 | *DLGAP2* | | |
| C | 1 | 40473197 | *NKAIN2* | Higher in A | |
| C | 1 | 68937675 | *C6orf167 to POU3F2* | Higher in A | BLOCK QTL 1q Quilter et al. [unpublished] |
| C | 1 | 69308215 | *FBXL4* | | |
| C | 1 | 260851292 | *ZNF246 to RAD23B* | None | |
| C | 3 | 114106868 | *NBAS to TRIB2* | Lower in A | |
| C | 11 | 12151392 | *RFXAP* | Higher in A | |
| C | 13 | 44399001 | *FOXP1* | Higher in A | |
| C | 14 | 31180400 | *KDM2B* | Lower in A | |
| C | 15 | 115259317 | *FARSB* | None | |
| C | 15 | 115517599 | *SGPP2, PAX3* | | BLOCK |
| C | 15 | 115603664 | *PAX3* | | |
| C | 15 | 117286727 | *SGPP3* | | |
| D | 1 | 62897862 | *MAP3K7 to EPHA7* | Higher in A | BLOCK QTL 1q Quilter et al. [unpublished] |
| D | 3 | 23436727 | *GPR139 to GPRC5B* | Higher in A | BP, PP Dick et al. [2002], Jones et al. [2007] |
| D | 3 | 24107618 | *CLEC19A to XYLT1* | | BLOCK |
| D | 3 | 24397779 | *XYLT1* | | |
| D | 3 | 25000000 | *XYLT1 to ABCC1* | | |
| D | 3 | 26271294 | *PARN* | Higher in A | BP, PP Dick et al. [2002], Jones et al. [2007] |
| D | 3 | 26502700 | *MKL2* | | |
| D | 3 | 26765413 | *ERCC4* | | BLOCK |
| D | 3 | 26800551 | *ERCC4 to SNX29* | | |
| D | 3 | 31977117 | *RBFOX1, MGRN1* | Higher in A | BLOCK |
| D | 3 | 86271637 | *KCNK12* | Lower in A | |
| D | 3 | 86384333 | *MSH2* | | |
| D | 3 | 98531389 | *CRIM1 to TMEM121* | Lower in A | BLOCK |
| D | 4 | 1958672 | *TRAPPC9* | Lower in A | |
| D | 4 | 4022957 | *FAM135B to KHDRBS3* | None | BLOCK |
| D | 5 | 9884000 | *LARGE* | None | |
| D | 6 | 108179295 | *FGGY* | None | |
| D | 7 | 131947563 | *PPP2R5C* | Higher in A | |
| D | 8 | 10777720 | *LCORL to SLIT2* | None | |
| D | 12 | 30900000 | *NOG to C12ORF67* | None | |
| D | 12 | 31605876 | *MSI2 to MRPS23* | Lower in A | |
| D | 12 | 41229732 | *RAB11FIP4* | None | |
| D | 12 | 41775108 | *WSB1 to KSR1* | | BLOCK |
| D | 12 | 56254231 | *CENPV* | Lower in A | |
| D | 12 | 56434716 | *NCOR1* | None | |
| D | 13 | 15439443 | *STT3B* | None | |
| D | 13 | 17730864 | *ARPP21* | None | |
| D | 13 | 129793183 | *NRIP1—C21ORF34* | Higher in A | |
| D | 13 | 145133007 | *POFUT2, ADARB1* | Higher in A | BLOCK |
| H | 5 | 5182280 | *MAP3K7IP1—SYNGR1* | Lower in A | |
| H | 11 | 44210118 | *DACH1—C13ORF37* | Lower in A | |

F_A indicates whether the frequency of haplotypes in a region showed a trend of being higher or lower in A (aggressive) animals. Genes shaded gray represent the presence of potential at risk haplotypes. The comment column indicates when there is a block of several consecutive haplotypes ($P < 0.0001$) and previously identified QTL.

**TABLE V. Summary of Regions of Significance ($P < 0.001$) Found by the Sliding Window Analysis in Common to More Than One Line**

| Lines | F_A | Highest *P* value | Chr | From bp | To bp | Gene(s) |
|---|---|---|---|---|---|---|
| B, C | None | 8.19E−05 | 1 | 14798237 | 15355428 | *SYNE1, ESR1* QTL 1p Quilter et al. [unpublished] |
| C, D | Higher in A | 8.54E−05 | 1 | 61936687 | 63800649 | *MAP3K7 to EPHA7* 1p Quilter et al. [unpublished] |
| B, D | None | 0.0002822 | 3 | 57283338 | 58614304 | *CTNNA2* |
| B, D | Higher in A | 0.0003314 | 3 | 91132479 | 91254239 | *MTA3* |
| C, D | None | 8.24E−05 | 3 | 98420696 | 99334429 | *CRIM1 to TMEM121* |
| C, D | None | 7.81E−05 | 4 | 5168635 | 5168635 | *KHDRBS3* |
| B, C | None | 6.62E−05 | 4 | 115401408 | 115416539 | *KIAA1324* |
| B, D | None | 0.0001147 | 10 | 22062023 | 23931957 | *NEK7, NR5A2, ZNF281, NAV1* Quilter et al. [2007] |
| B, D | None | 0.0003024 | 13 | 121289653 | 122262655 | *EPHA6, PROS1, POU1F1* |
| B, D | Higher in A | 9.85E−05 | 13 | 125764540 | 128597138 | *GBE1, ROBO1, ROBO2* |

F_A indicates whether the frequency of haplotypes in a region showed a trend of being higher or lower in A (aggressive) animals. Genes shaded gray represent the presence of potential at risk haplotypes.

## The Most Consistent Candidate Region Across All Analyses and All Breeds—A Candidate Region for Puerperal Psychosis and Bipolar disorder

From all of the candidate regions the most interesting appears to be the large region on SSC3, which was consistent across six analyses. This region had the highest significance in more than one analysis, was present in all four lines and is a region rich in genes associated with psychiatric disorders. The sliding window analysis also identified haplotypes that were higher in infanticide animals.

Within this interval there were two peak regions. The first at 23.4 Mb was the top SNP, from the single SNP association analysis and mapped to the region between *GPR139* and *IQCK*. Edenberg et al. [1997] found evidence of linkage in this region in humans with BP, which was within 1Mb of this peak and was confirmed by Dick et al., [2002]. About 50% of female patients within these cohorts did exhibit postpartum symptoms. There are several candidate genes in and around this region. The most interesting is *GPR139*: this gene is a G-protein-coupled receptor, important in signal transduction. Predominant expression of mouse *GPR139* is in putamen, medulla and caudate nucleus with a lesser expression in thalamus, amygdala and spinal cord [Süsens et al., 2006]. These areas of the CNS are involved in mood, behaviour and locomotion activity. It also shares identity with an odorant-like gene derived from human erythroid cells [Vanti et al., 2003]. A study using evolutionary relationships between species and nucleotide sequences placed *GPR139* into the same group as somatostatin receptors [Gloriam et al., 2005]. Somatostatin is important for regulating the release of other hormones. This suggests that there may be a link between this gene and changing hormone levels after giving birth, which is potentially a trigger for abnormal maternal behavior.

There are several other candidate genes and regions (*XYLT2* to *ABCC1*; *SYT17*; *PARN*; *MLK2*; *ERCC4*; *SHISA9*) in this interval, with connections to attention-deficit hyperactivity disorder (ADHD), alcoholism, Autism, Alzheimer's disease, conduct disorder and schizophrenia. Their detailed functions are summarized in supplementary Tables III and V. It is unclear whether these genes act separately or are linked together to contribute to the porcine maternal infanticide phenotype.

The second peak on SSC3 at 31.9 Mb, mapped to the region between *RBFOX1* and *UBN1* and is of particular significance as it is syntenic with the human puerperal psychosis region (16p13) proposed by Jones et al. [2007] and within 2 Mb of a peak region linked to bipolar disorder [Ewald et al., 2002]. Twenty-one SNPs ($P < 0.01$) were present in this region or *RBFOX1* itself. These two genes are therefore important candidates:

RBFOX1: This gene binds to the C-terminus of ataxin-2 and may contribute to the restricted pathology of spinocerebellar ataxia type 2 (SCA2). Ataxin-2 is the gene product of the SCA2 gene, which causes familial neurodegenerative diseases [Shibata et al., 2000]. *RBFOX1* is also associated with movement-related adverse antipsychotic effects for conduct disorder [Aberg et al., 2010]. A female with autism, epilepsy and global developmental delay was found to have a de novo translocation involving chromosomes 15 and 16 resulting in a cryptic deletion in *RBFOX1* and reduced gene expression was also confirmed by Q-PCR, indicating that this is a good candidate for autism [Martin et al., 2007]. Also, in a CNV study, rare inherited structural variations were found that implicated a set of putative candidate genes for further study in the etiology of ADHD, which included *RBFOX1* [Elia et al., 2010]. SNPs present in the human syntenic region, in and around *RBFOX1*, are associated with BP, autism, Alzheimer's, and ADHD with hyperactivity and conduct disorder [Mailman et al., 2007; Anney et al., 2008]. *RBFOX1* is also a key modulator of alternative splicing in neuronally expressed genes including *GRIN1* [Lee et al., 2009]; defects in *GRIN1* have been linked to psychiatric disorders [Cherlyn et al., 2010] and this gene was found to be differentially expressed in porcine maternal infanticide [Quilter et al., 2008].

UBN1: This gene may also be important as it maps to a region investigated for autism in humans [Barnby et al., 2005].

The block haplotype LD analysis showed that the two regions on SSC3 are not in linkage disequilibrium and thus represent two loci. This confirms the suggestion by Jones et al. [2007] that there appears to be at least two loci present, containing genes relevant to various forms of bipolar disorder. In addition, as this region is consistently one of the top regions in our analyses and had SNPs significant in all four lines, this supports our hypothesis that maternal infanticide in pigs is a good animal model for human puerperal psychosis.

**TABLE VI. Top Haplotype LD Results (Shaded Log10P Results Indicates the Two Regions Which Reached GWS)**

| Lines in region | CHR | Line | Haplotype | F_A | F_U | CHI SQ | DF | P | SNPS | Start | Finish | Log10P | Gene |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| B,C,(D),H | 1 | B | AAGAG | 0.08571 | 0.297 | 14.98 | 1 | 0.0001088 | ALGA0001317 \| DRGA0000174 \| H3GA0000934 \| ALGA0001327 \| ALGA0001328 | 16370845 | 16445454 | 3.9633711 | *PLEKHG1* |
| C,D,(H) | 1 | D | AGAAAGAAA | 0.8838 | 0.6386 | 16.34 | 1 | 5.30E−05 | MARC0013135 \| ALGA0003751 \| ASGA0003097 \| ASGA0003100 \| MARC0052892 \| ALGA0110077 \| ALGA0115579 \| ASGA0003102 \| ALGA0003761 | 61499482 | 61847884 | 4.276134 | *MAP3K7* |
| | 1 | C | GAAGAAA | 0.1705 | 0 | 16.04 | 1 | 6.20E−05 | ALGA0003975 \| DRGA0001106 \| ASGA0003239 \| INRA0002726 \| ASGA0003244 \| MARC0075306 \| ALGA0003981 | 68730879 | 69128641 | 4.2079587 | *MMS22L* to *POU3F2* |
| | 1 | C | GAAAA | 0.173 | 0 | 16.3 | 1 | 5.39E−05 | ALGA0003988 \| MARC0027154 \| ASGA0003249 \| INRA0002742 \| ALGA0003991 | 69150208 | 69205895 | 4.2680891 | *MMS22L* to *POU3F2* |
| | 1 | C | GCAAGCAGA | 0.1558 | 0 | 14.53 | 1 | 0.0001379 | ALGA0004000 \| ASGA0003261 \| ALGA0004005 \| ALGA0004006 \| ALGA0004007 \| ASGA0003265 \| ALGA0119247 \| H3GA0052986 \| ASGA0100874 | 69308215 | 69552862 | 3.8604357 | 5′ *FBXL4* |
| B,(C),D,H | 3 | D | AA | 0.3725 | 0.12 | 17.29 | 1 | 3.21E−05 | ALGA0113238 \| MARC0010219 | 24107618 | 24118678 | 4.4940365 | *SYT17* to *XYLT1* |
| | 3 | D | GG | 0.37 | 0.12 | 16.89 | 1 | 3.95E−05 | ALGA0018155 \| ALGA0018160 | 24518891 | 24532739 | 4.4031831 | *XYLT1* |

(*Continued*)

**TABLE VI. (*Continued*)**

| Lines in region | CHR | Line | Haplotype | F_A | F_U | CHI SQ | DF | P | SNPS | Start | Finish | Log10P | Gene |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 3 | D | GGGGAGGAGGCAA | 0.26 | 0.05051 | 16.6 | 1 | 4.61E−05 | MARC0014659 \| DIAS0000928 \| ALGA0018228 \| ALGA0018230 \| ASGA0014039 \| ASGA0014038 \| ASGA0090872 \| ALGA0106890 \| ALGA0114830 \| ASGA0014055 \| ALGA0018260 \| MARC0001955 \| ASGA0014064 | 26054297 | 26531777 | 4.3362991 | *PARN* to *MKL2 (MAP3K10)* (MIR365A and MIR193B) |
| | 3 | D | GGGG | 0.2549 | 0.05 | 16.32 | 1 | 5.35E−05 | H3GA0009171 \| ALGA0018311 \| ALGA0018313 \| ALGA0018331 | 26845421 | 27012951 | 4.2714028 | *ERCC4* to *SHISA9* |
| (B),C,D,H | 3 | D | AGGG | 0.3431 | 0.11 | 15.61 | 1 | 7.80E−05 | H3GA0055035 \| MARC0073946 \| ALGA0102473 \| ASGA0092767 | 31848979 | 32177080 | 4.1078497 | 5′ *RBFOX1* |
| D | 3 | D | GACGAA | 0.2059 | 0.01061 | 19.79 | 1 | 8.64E−06 | DIAS0000405 \| ASGA0015374 \| H3GA0010102 \| ALGA0020145 \| ALGA0020149 \| SIRI0000186 | 87502097 | 87622338 | 5.0636371 | *EPAS1* |
| | 3 | C | AA | 0.6818 | 0.9186 | 15.18 | 1 | 9.79E−05 | ASGA0098921 \| MARC0098920 | 114104190 | 114106868 | 4.0090842 | *NBAS* to *TRIB2 in LINC00276* |
| | 4 | D | OMNIBUS | NA | NA | 25.98 | 5 | 8.99E−05 | ALGA0022018 \| ASGA0017024 \| MARC0062117 \| ASGA0017039 \| ASGA0017041 \| ASGA0017047 \| MARC0084013 \| MARC0034221 \| ASGA0017054 | 1289092 | 1537373 | 4.0464336 | *PTK2* to *DENND3* |
| D | 4 | D | GAAAAA | 0.12 | 0.4141 | 22.03 | 1 | 2.69E−06 | DRGA0004385 \| MARC0058451 \| DRGA0004390 \| ALGA0022450 \| ASGA0017526 \| DRGA0004397 | 4046035 | 4211845 | 5.5707323 | *KHDRBS3* to *FAM135B* |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 4 | D | OMNIBUS | NA | NA | 31.31 | 7 | 5.45E−05 | DRGA0004385 \| MARC0058451 \| DRGA0004390 \| ALGA0022450 \| ASGA0017526 \| DRGA0004397 | 4046035 | 4211845 | 4.2634442 | *KHDRBS3* to *FAM135B* |
| B,C | 4 | B | AAGAGAGAA | 0.2075 | 0.01961 | 17.99 | 1 | 2.22E−05 | DIAS0004198 \| ALGA0028142 \| ASGA0022124 \| MARC0070819 \| ASGA0022128 \| INRA0016711 \| MARC0095172 \| ASGA0022140 \| ALGA0028166 | 115468034 | 115679812 | 4.6530605 | *TMEM167B*, *TAF13*, *WDR47*, *CLCC1*, *AKNAD1*, *GPSM2* |
| | 4 | B | OMNIBUS | NA | NA | 26.14 | 4 | 2.97E−05 | DIAS0004198 \| ALGA0028142 \| ASGA0022124 \| MARC0070819 \| ASGA0022128 \| INRA0016711 \| MARC0095172 \| ASGA0022140 \| ALGA0028166 | 115468034 | 115679812 | 4.5278289 | *TMEM167B*, *TAF13*, *WDR47*, *CLCC1*, *AKNAD1*, *GPSM2* |
| D | 6 | D | AAGA | 0.1078 | 0.34 | 15.72 | 1 | 7.35E−05 | ALGA0034885 \| ALGA0034874 \| DRGA0006563 \| ALGA0034871 | 16125649 | 16204670 | 4.1336536 | *CDH11(8)* to *GOT2* |
| | 10 | D | GG | 0.4804 | 0.22 | 15.02 | 1 | 0.0001064 | ASGA0046260 \| H3GA0029136 | 8333694 | 8353567 | 3.9730584 | *GPATCH2* to *TGFB2* |
| D,H | 12 | D | AA | 0.2157 | 0.4896 | 16.34 | 1 | 5.29E−05 | H3GA0052480 \| M1GA0016607 | 31605876 | 31611387 | 4.2764622 | MSI2 to MRPS23 CUEDC1 |
| B,D | 12 | D | AA | 0.3529 | 0.66 | 19.05 | 1 | 1.28E−05 | MARC0062541 \| ALGA0107852 | 56062762 | 56072709 | 4.8941493 | *ZNF287* to *ZNF624* |
| | 12 | D | GG | 0.5392 | 0.26 | 16.39 | 1 | 5.16E−05 | MARC0062541 \| ALGA0107852 | 56062762 | 56072709 | 4.2875187 | *ZNF287* to *ZNF624* |
| | 12 | D | OMNIBUS | NA | NA | 19.66 | 2 | 5.38E−05 | MARC0062541 \| ALGA0107852 | 56062762 | 56072709 | 4.2695407 | *ZNF287* to *ZNF624* |
| | 12 | D | GGGGGGAA | 0.2843 | 0.56 | 15.75 | 1 | 7.24E−05 | H3GA0035053 \| MARC0089347 \| MARC0065270 \| H3GA0035071 \| ALGA0067281 \| ALGA0067282 \| H3GA0035082 \| H3GA0035061 | 56254231 | 56492618 | 4.1400815 | *ADORA2B*, *ZSWIM7*, *TTC19*, *NCOR1* |

(*Continued*)

TABLE VI. (*Continued*)

| Lines in region | CHR | Line | Haplotype | F_A | F_U | CHI SQ | DF | P | SNPS | Start | Finish | Log10P | Gene |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 13 | D | AACGAG | 0.2647 | 0.06122 | 15.02 | 1 | 0.0001064 | ALGA0068783 \| ALGA0068784 \| ALGA0068790 \| ASGA0056621 \| MARC0005330 \| MARC0050907 | 17773577 | 17983970 | 3.9730584 | *ARPP21* |
| B,C,D | 13 | D | GGGA | 0.2059 | 0.02 | 17.29 | 1 | 3.205E−05 | ASGA0060288 \| MARC0043234 \| M1GA0017995 \| M1GA0017997 | 145074268 | 145176604 | 4.494172 | 5′ *ADARB1*, *POFUT2* |
| | 13 | D | GGGA | 0.2059 | 0.02 | 17.29 | 1 | 3.205E−05 | ASGA0060288 \| MARC0043234 \| M1GA0017995 \| M1GA0017997 | 145074268 | 145176604 | 4.494172 | 5′ *ADARB1*, *POFUT2* |
| | 13 | D | OMNIBUS | NA | NA | 21.67 | 3 | 7.642E−05 | ASGA0060288 \| MARC0043234 \| M1GA0017995 \| M1GA0017997 | 145074268 | 145176604 | 4.116793 | 5′ *ADARB1*, *POFUT2* |
| | 13 | D | OMNIBUS | NA | NA | 21.67 | 3 | 7.642E−05 | ASGA0060288 \| MARC0043234 \| M1GA0017995 \| M1GA0017997 | 145074268 | 145176604 | 4.116793 | 5′ *ADARB1*, *POFUT2* |
| D | 14 | D | GAGGA | 0.5 | 0.8 | 19.94 | 1 | 8.003E−06 | MARC0049055 \| M1GA0018418 \| ALGA0076284 \| M1GA0018417 \| ALGA0076263 | 22794071 | 22911648 | 5.0967472 | *FBRSL1* to *GALNT9* |
| | 14 | D | OMNIBUS | NA | NA | 21.23 | 3 | 9.41E−05 | MARC0049055 \| M1GA0018418 \| ALGA0076284 \| M1GA0018417 \| ALGA0076263 | 22794071 | 22911648 | 4.0264104 | *FBRSL1* to *GALNT9* |
| B,D | 15 | D | AGAGAAAGA | 0.07731 | 0.2947 | 15.76 | 1 | 7.206E−05 | ALGA0084037 \| ALGA0084043 \| ASGA0068714 \| ASGA0068711 \| CASI0008608 \| ALGA0084057 \| ASGA0095872 \| ASGA0104534 \| ALGA0084052 | 13428035 | 13797461 | 4.1423057 | *THSD7B* to *CXCR4* |

| | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| D | 15 | D | AAAAA | 0.01961 | 0.1871 | 15.4 | 1 | 8.697E−05 | MARC0044987 | 110869659 | 110986239 | 4.0606305 | *ATIC, FN1* |
| | | | | | | | | | MARC0012403 | | | | |
| | | | | | | | | | ASGA0070468 | | | | |
| | | | | | | | | | MARC0062252 | | | | |
| | | | | | | | | | DIAS0000510 | | | | |
| | | | | | | | | | ASGA0070474 | | | | |
| C | 15 | C | GGGAGA | 0.3908 | 0.08235 | 22.53 | 1 | 2.068E−06 | ALGA0087273 | 115517599 | 115667301 | 5.6844495 | 3′ *PAX3* |
| | | | | | | | | | H3GA0045081 | | | | |
| | | | | | | | | | ASGA0070769 | | | | |
| | | | | | | | | | M1GA0020474 | | | | |
| | | | | | | | | | ASGA0070779 | | | | |
| | | | | | | | | | MARC0004065 | | | | |
| H | 18 | H | GA | 0.6957 | 0.8939 | 16.14 | 1 | 5.89E−05 | MARC0037341 | 8999992 | 9018459 | 4.2295899 | *TMEM213* |
| | | | | | | | | | ALGA0097013 | | | | |
| C,D | 18 | D | AGAAA | 0 | 0.1717 | 18.95 | 1 | 1.34E−05 | ALGA0115113 | 15173938 | 15529609 | 4.8732194 | *PLXNA4* to *PODXL* |
| | | | | | | | | | MARC0064624 | | | | |
| | | | | | | | | | ALGA0107322 | | | | |
| | | | | | | | | | H3GA0050474 | | | | |
| | | | | | | | | | ALGA0097253 | | | | |

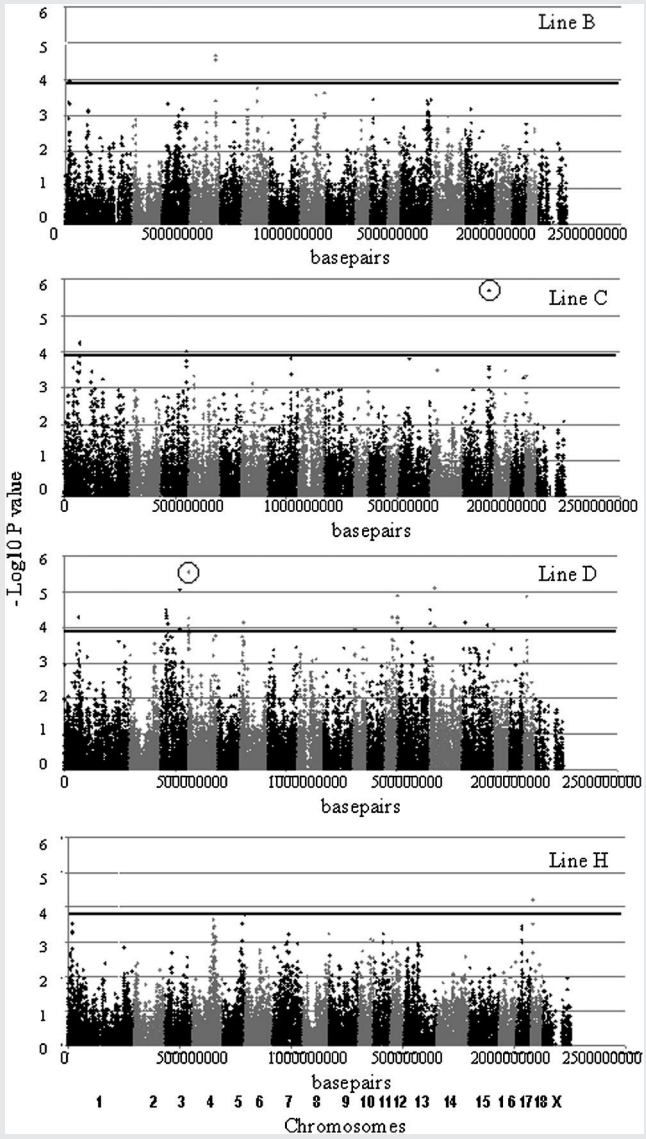


**FIG. 2. Haplotype LD results for all lines (B, C, D, H). Regions with a $\chi 2$ value $>14.4$ (1 df; equivalent to a *P* value $< 0.0001$) corresponding to $-\log10P > 3.85$ are above the solid line. The regions of GWS are highlighted inside a circle on chromosome 4, line D (*KHDRBS3* to *FAM135B)* and chromosome 15, line C (*PAX3*).**

## Other Puerperal Psychosis Candidate Regions

The other candidate region proposed by Jones et al. [2007] for PP was syntenic to SSC4. This region had top gene/s, which survived 348,500 permutations and blocks (*GSMDC1* to *MYC*) came up in the hayplotype/LD analysis although with only moderate p values. The human study by Mahon et al. [2009] found associations of increased susceptibility to postpartum mood symptoms with two genes, *METTL13* and *HMCN1*. *METTL13* was within a significant block syntenic to SSC9 having top gene/s, which survived one million permutations but *HMCN1* was just outside this region.

**TABLE VII. Summary of All Analyses**

| QTL | Quilter et al. [2007]/ Jones et al. [2007]/ Dick et al. [2002]/ Chen et al. [2009]/ Mahon et al., 2009 | Confirmation of QTL from previous studies by association analysis | Top association analysis (Log10 emp>4, 4 lines, 1 mill perm) | Survived 1 mill permutations (adaptive and not in previous column) | Max (T) permutation testing ++ = $P < 1$, + = $P = 0.8$ –0.4, + = $P < 0.04$ | Sliding window Ihaplotype $P < 0.0001$ | SW lines in common $P < 0.001$ | Haploype/LD analysis chi2 $P < 0.0001$ log10P > 3.85, >5.5 and GWS in bold | Number of analyses | Peak/Key genes, genes in bold have psychiatric and/or neurolgical connection (DAVID, NCBI), shaded when genes present in more than one analysis |
|---|---|---|---|---|---|---|---|---|---|---|
| 3 (BP, PP) | + | + | + | | + | D | | + | 6 | ***GPR139*** *TO IQCK,* ***SYT17*** *TO XYLT1, XYLT1 TO ABCC1, MKL2,* ***ERCC4*** *TO SNX29,* ***RBFOX1*** |
| 1 p Quilter | + | | | | + | B | + | + | 5 | ***SYNE1, ESR1, STXBP5*** *TO C6ORF103,* ***UST*** |
| 1 p Quilter | + | + | | | + | C,D | + | + | 5 | ***MAP3K7****, MAP3K7 TO EPHA7,* ***EPHA7*** *TO* ***POU3F2****,* ***POU3F2 TO FBXL4, FBXL4****, RIMS1 TO KCNQ5, HDAC TO FRK, LIPC TO AQP9, THBS1 TO RASGRP1* |
| 4a new | | | + | | + | D | + | + | 5 | *FAM135B TO* ***KHDRBS3****, PARP10 TO DENND3, DENND3,* ***KHDRBS3*** *TO ZFAT,* ***SYT17 TO XYLT1****, PARN, BFAR,* ***MKL2****,* ***ERCC4*** *TO SNX29,* ***PTK2*** *TO DENND3* |
| 4b new | | | + | | + | B | + | + | 5 | *WDR47, CLCC1, CLCC1 TO AKNAD1, KCNA3 TO PROK1, SLC6A17,* ***TMEM167B****, TAF13 TO WDR47, AKNAD1, GPSM2* |
| 13b new | | | + | | + | B, D | + | + | 5 | ***ADARB1, POFUT2, PRSS7, PROS1, POU1F1****, GBE1 TO* ***ROBO1, ROBO1, ROBO2, ROBO1 TO LIPI*** |
| 10 Quilter | + | + | | + | ++ | | + | | 4 | *NEK7,* ***NR5A2, NAV1****, CNTFR, GALT TO ARID3C, ZNF438 TO ZEB1, SVIL TO ZNF438, CUBN, PDSS1, STAM, FAM107B, FAM107B TO FRMD4A, FRMD4A, MYO3A TO PDSSI* |
| 13a new | | + | | | + | D | | + | 4 | *STT3B, ARPP21* |
| 1q new | | + | | | ++ | C | | | 3 | *COL5A1 TO PAEP, ZNF462 TO RAD23B* |
| 2 Chen | + | + | | + | ++ | | | | 3 | *ZNF474 TO* ***SNCAIP****, FER, ATG12 TO SEMA6A, LOX TO ZNF474* |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| 6 Chen | + | + | | | ++ | | | + | 3 | *TOX3 TO SALL1,* ***CDH11*** *TO GOT2* |
| 6 new | | | + | | ++ | D | | | 3 | ***FGGY****, FOXE3, TESK2, SGIP1* |
| 12a new | | | | + | + | | | + | 3 | *NOG to C17orf67, MS12 TO MRPS23, GDPD1, ADORA2B, ZSWIM7, TTC19* |
| 12c new | | | | + | + | | | + | 3 | *ZNF624, ZNF287, ALOX15 TO SENP3, NCOR1* |
| 14 new | | | | + | + | | | + | 3 | ***GALNT9****, FBRSL1 TO GALANT9* |
| 18a new | | | | + | + | | | + | 3 | *PLXNA4 TO PODXL, KLHDC10* |
| 4 (PP) | + | | | | ++ | | | | 2 | *GSMDC1 TO* ***MYC, ASAP1*** |
| 9 Mahon | + | + | | + | | | | | 2 | ***NRCAM, HMCN1****, ORC5L TO LHFPL3, CNTNAP2* |
| 14 Chen | + | | | | ++ | | | | 2 | *BUB3, HMX3,* ***HTRA1, ATRNL1*** |
| 15 Chen | + | + | | | + | | | | 2 | ***GTDC1****, THSD7B* ***TO CXCR4*** |
| 15c | | | | | + | | | + | 2 | ***SGPP2 TO PAX3, PAX3, CCDC140*** |
| Xp Quilter, Chen | + | + | | | ++ | | | | 2 | ***MAOA, SCML2 TO CDKL5****, FRMPD4, PRPS2, ZNF630 TO TFE3* |
| 1q Mahon | + | | | | | | | | 1 | *TYRP1 TO PTPRD* |
| 2 Quilter | + | | | | | | | | 1 | *GPR98, MEF2C, ARRDC3 TO NR2F1* |
| 2 new | | | + | | | | | | 1 | *KIF3A TO SEPT8* |
| 8 new | | | + | + | | | | | 1 | ***GRID2 TO FAM190A****, FAM190A, WDFY3, CDS1 TO NKX6-1, XKX6 TO AGPAT9, ENOPH1* |
| 15b | | | | | + | | | + | 1 | ***ATIC, FN1, ERBB4*** |
| 18b new | | | | | + | | | + | 1 | ***TMEM213*** |
| Xq Quilter, Chen | + | | | | ++ | | | | 1 | *GPC3, VBP1* |

However, four SNPs within *HMCN1* with an association significance of $P < 0.01$ were present (top SNP: −log10emp 3.0712, 42,724 permutations). The other region of significance described by Mahon et al. [2009] was syntenic to SSC1 at 219.5 Mb. Our analyses did not reveal significant associations in this region.

## Regions of GWS

Two regions reached genome wide significance from our block haplotype/LD analysis, one on SSC4 (4a) in one Duroc based line (D) and one on SSC15 in two lines, one Large White and one Duroc based (C, D).

The gene region on SSC4(a) contains some good candidate genes:

*FAM135B* to *KHDRBS3*: SNPs in the intergenic region between *FAM135B* and *KHDRBS3* are associated with Parkinson's, neurotic disorders and cognition in humans [Fung et al., 2006; Van den Oord et al., 2008; Cirulli et al., 2010].

*PTK2*: Down regulation of this gene is associated with autism in humans [Wei et al., 2011].

*KCNK9*: This gene encodes a member of the superfamily of potassium channel proteins containing two pore-forming P domains, and is highly expressed in the cerebellum. It is imprinted in human and mouse fetal brain, with preferential expression from the maternal allele. It is mutated in a maternally transmitted genomic-imprinting syndrome of mental retardation, Birk Barel mental retardation dimorphism syndrome [Barel et al., 2008]. This is an interesting candidate as heritability of maternal infanticide is higher from dam to daughter than sire to daughter [Knap and Merks, 1987; Van der Steen et al., 1988] suggesting that maternal imprinting could play a part in the phenotype.

The second region that reached genome wide significance (−log10P 5.68) on SSC15 contained a couple of good candidate genes:

*PAX3*: The most significant haplotype in this interval was 3' to and within *PAX3*. Three SNPs from this region also had a *P* value of 0.07978 from the max(T) permutation analysis, with a further 4 SNPs with *P* values 0.1376–0.249 representing the interval from *SGPP2* to *PAX3*. This was the largest block of SNPs from this analysis where all SNPs had a *P* value <0.4. This gene has a critical role in fetal development. In mice, *PAX3* mutations lead to spina bifida and exencephaly suggesting a role in normal neural development [Epstein et al., 1993]. In humans, mutations in *PAX3* contribute to the pigmentation and auditory problems of Waardenburg syndrome [Tassabehji et al., 1992] and are also associated with craniofacial-deafness-hand syndrome [Asher et al., 1996].

*EPHA4*: Another gene in this region and is a further member of the epharin receptor family, which has been implicated in mediating developmental events, particularly in the nervous system (Wilkinson, 2001). In neuroimaging study of AD, which measured gray matter (GM) density, volume, and cortical thickness from baseline scans in humans, *EPHA4* was found to have GWA with multiple brain regions [Shen et al., 2010].

## Other Significant Regions Detected in This Study

Other regions that were concordant across multiple analyses were present on SSC4 (4b) and SSC13 (13a and 13b). The region SSC13b had interesting results from the sliding window analysis as the haplotype across *GBE1*, *ROBO1*, and *ROBO2* was more frequent in infanticide animals than controls. Functions of candidate genes from all these regions are summarized in supplementary Tables III and V.

## Confirmation of Previously Identified QTL

Confirming previously identified porcine maternal infanticide QTL (1, 10, X, 2, 6, 15) helped to verify our current results and of these, regions on chromosomes 1 and 10 were the strongest (Supplementary Table IV).

The region on 1p persisted throughout multiple analyses. Several genes are of interest and are discussed in supplementary Table III. In particular SNPs in *SYNE1* were of moderate significance (although not at the genome wide level) in a meta-analysis of genome-wide association (GWA) data of human BP and major depressive disorder (MDD). *SYNE1* also contains a spectrin-binding domain, suggesting a connection with the function of the BP susceptibility locus *ANK3* [Liu et al., 2011]. Additionally, *UST* and the region *UST* to *SASH1* contained SNPs ($P < 0.01$) that were common to 3 lines (B, C, H) and represented the largest block of common contiguous SNPs in this analysis. In a human GWA study looking at the pharmacogenetics of antidepressants, drug-specific analyses revealed a genome-wide significant association between marker rs2500535 in *UST* and response to nortriptyline, an antidepressant [Uher et al., 2010]. The second region on SSC1 which was on the long arm (1q) was particularly interesting because a large block of SNPs had alleles, although at a low frequency, which were only present in the affected animals. The function of candidate genes (*POU3F2*; *MAP3K7*), from this region are discussed in supplementary Table III. For SSC10, three significant regions were identified in the range of our previously reported QTL [Quilter et al., 2007] and the sliding window analysis confirmed the peak region from our previous work (22.1 Mb) [Quilter et al., 2007]. The function of interesting genes in this region are summarized in supplementary Table V.

## CONCLUSION

In conclusion, this study has confirmed and refined our previous work and has additionally implicated more potential genetic regions likely to be involved in porcine maternal infanticide. By analyzing the data in different ways we have rationalized our results and have highlighted regions containing candidate genes worthy of further investigation, to confirm their role in the abnormal phenotype. Interestingly, some of our top SNPs fall within intergenic regions and we have noted that some of these intervals contain non-coding RNA, which are known to be important in regulating gene expression in neural tissue [Lin et al., 2011]. The region on SSC3 was one of the most consistent and interesting of all our results as it is syntenic to a proposed puerperal psychosis region in humans on 16p, as well as being a region with moderate linkage to bipolar disorder. There appears to be at least two loci present in this region, containing genes relevant to various forms of bipolar disorder. Our findings add significant weight to our hypothesis that porcine maternal infanticide would be a good animal model for human

puerperal psychosis, providing readily available tissue for future studies of this complex disease. Further studies in both pigs and humans looking for gene polymorphisms associated with infanticide/PP, by sequencing candidate genes, could lead to diagnostic tests for both conditions and to a greater understanding of the genetic pathways linked to them.

## ACKNOWLEDGMENTS

The authors would like to thank the Pig Improvement Company (PIC) part of Genus for the provision of animal DNA samples.

## REFERENCES

Aberg K, Adkins DE, Bukszár J, Webb BT, Caroff SN, Miller del D, Sebat J, Stroup S, Fanous AH, Vladimirov VI, McClay JL, Lieberman JA, Sullivan PF, van den Oord EJ. 2010. Genome wide association study of movement-related adverse antipsychotic effects. Biol Psychiatry 67(3):279–282.

Ahlström S, Jarvis S, Lawrence AB. 2002. Savaging gilts are more restless and more responsible to piglets during expulsive phase parturition. Appl Anim Behav Sci 76:83–91.

Ahn S, Costa J, Emanuel J. 1996. PicoGreen quantitation of DNA: Effective evaluation of samples pre-or post-PCR. Nucl Acids Res 24(13):2623–2625.

Anitha A, Nakamura K, Yamada K, Suda S, Thanseem I, Tsujii M, Iwayama Y, Hattori E, Toyota T, Miyachi T, Iwata Y, Suzuki K, Matsuzaki H, Kawai M, Sekine Y, Tsuchiya K, Sugihara G, Ouchi Y, Sugiyama T, Koizumi K, Higashida H, Takei N, Yoshikawa T, Mori N. 2008. Genetic analyses of roundabout (ROBO) axon guidance receptors in autism. Am J Med Genet (Neuropsychiatr Genet) 147(7):1019–1027.

Anney RJ, Lasky-Su J, O'Dúshláine C, Kenny E, Neale BM, Mulligan A, Franke B, Zhou K, Chen W, Christiansen H, Arias-Vásquez A, Banaschewski T, Buitelaar J, Ebstein R, Miranda A, Mulas F, Oades RD, Roeyers H, Rothenberger A, Sergeant J, Sonuga-Barke E, Steinhausen H, Asherson P, Faraone SV, Gill M. 2008. Conduct disorder and ADHD: Evaluation of conduct problems as a categorical and quantitative trait in the international multicentre ADHD genetics study. Am J Med Genet (Neuropsychiatr Genet) 147(8):1369–1378.

Asher JH Jr, Harrison RW, Morell R, Carey ML, Friedman TB. 1996. Effects of *PAX3* modifier genes on craniofacial morphology, pigmentation, and viability: A murine model of Waardenburg syndrome variation. Genomics 34:285–298.

Baranzini SE, Srinivasan R, Khankhanian P, Okuda DT, Nelson SJ, Matthews PM, Hauser SL, Oksenberg JR, Pelletier D. 2010. Genetic variation influences glutamate concentrations in brains of patients with multiple sclerosis. Brain 133(9):2603–2611.

Barel O, Shalev SA, Ofir R, Cohen A, Zlotogora J, Shorer Z, Mazor G, Finer G, Khateeb S, Zilberberg N, Birk OS. 2008. Maternally inherited Birk Barel mental retardation dysmorphism syndrome caused by a mutation in the genomically imprinted potassium channel *KCNK9*. Am J Hum Genet 83(2):193–199.

Barnby G, Abbott A, Sykes N, Morris A, Weeks DE, Mott R, Lamb J, Bailey AJ, Monaco AP. 2005. International Molecular Genetics Study of Autism Consortium. Candidate-gene screening and association analysis at the autism-susceptibility locus on chromosome 16p: Evidence of association at *GRIN2A* and *ABAT*. Am J Hum Genet 76(6):950–966.

Chen C, Gilbert C, Yang G, Guo Y, Segonds-Pichon A, Ma J, Evans G, Brenig B, Sargent C, Affara N. 2008. Maternal infanticide in sows: Incidence and behavioural comparisons between savaging and non-savaging sows at parturition. Appl Anim Behav Sci 109:238–248.

Chen C, Guo Y, Yang G, Yang Z, Zhang Z, Yang B, Yan X, Perez-Enciso M, Ma J, Duan Y, Brenig B, Huang L. 2009. A genome wide detection of quantitative trait loci on pig maternal infanticide behavior in a large scale White Duroc × Erhualian resource population. Behav Genet 39(2):213–219.

Cherlyn SY, Woon PS, Liu JJ, Ong WY, Tsai GC, Sim K. 2010. Genetic association studies of glutamate, GABA and related genes in schizophrenia and bipolar disorder: A decade of advance. Neurosci Biobehav Rev 34(6):958–977.

Cirulli ET, Kasperaviciūte D, Attix DK, Need AC, Ge D, Gibson G, Goldstein DB. 2010. Common genetic variation and performance on standardized cognitive tests. Eur J Hum Genet 18(7):815–820.

Cottrell JR, Borok E, Horvath TL, Nedivi E. 2004. CPG2: A brain- and synapse-specific protein that regulates the endocytosis of glutamate receptors. Neuron 44(4):677–690.

Coy JF, Wiemann S, Bechmann I, Bächner D, Nitsch R, Kretz O, Christiansen H, Poustka A. 2002. Pore membrane and/or filament interacting like protein 1 (POMFIL1) is predominantly expressed in the nervous system and encodes different protein isoforms. Gene 290(1–2):73–94.

Davis OS, Butcher LM, Docherty SJ, Meaburn EL, Curtis CJ, Simpson MA, Schalkwyk LC, Plomin R. 2010. A three-stage genome-wide association study of general cognitive ability: Hunting the small effects. Behav Genet 40(6):759–767.

De Jager PL, Jia X, Wang J, de Bakker PI, Ottoboni L, Aggarwal NT, Piccio L, Raychaudhuri S, Tran D, Aubin C, Briskin R, Romano S, Baranzini SE, McCauley JL, Pericak-Vance MA, Haines JL, Gibson RA, Naeglin Y, Uitdehaag B, Matthews PM, Kappos L, Polman C, McArdle WL, Strachan DP, Evans D, Cross AH, Daly MJ, Compston A, Sawcer SJ, Weiner HL, Hauser SL, Hafler DA, Oksenberg JR, International MS Genetics Consortium. 2009. Meta-analysis of genome scans and replication identify *CD6*, *IRF8* and *TNFRSF1A* as new multiple sclerosis susceptibility loci. Nat Genet 41(7):776–782.

Dick DM, Foroud T, Edenberg HJ, Miller M, Bowman E, Rau NL, DePaulo JR, McInnis M, Gershon E, McMahon F, Rice JP, Bierut LJ, Reich T, Nurnberger J Jr. 2002. Apparent replication of suggestive linkage on chromosome 16 in the NIMH genetics initiative bipolar pedigrees. Am J Med Genet 114(4):407–412.

Dick DM, Aliev F, Krueger RF, Edwards A, Agrawal A, Lynskey M, Lin P, Schuckit M, Hesselbrock V, Nurnberger J Jr, Almasy L, Porjesz B, Edenberg HJ, Bucholz K, Kramer J, Kuperman S, Bierut L. 2011. Genome-wide association study of conduct disorder symptomatology. Mol Psychiatry 16(8):800–808.

Edenberg HJ, Foroud T, Conneally PM, Sorbel JJ, Carr K, Crose C, Willig C, Zhao J, Miller M, Bowman E, Mayeda A, Rau NL, Smiley C, Rice JP, Goate A, Reich T, Stine OC, McMahon F, DePaulo JR, Meyers D, Detera-Wadleigh SD, Goldin LR, Gershon ES, Blehar MC, Nurnberger JI Jr. 1997. Initial genomic scan of the NIMH genetics initiative bipolar pedigrees: Chromosomes 3, 5, 15, 16, 17, and 22. Am J Med Genet 74(3):238–246.

Edenberg HJ, Koller DL, Xuei X, Wetherill L, McClintick JN, Almasy L, Bierut LJ, Bucholz KK, Goate A, Aliev F, Dick D, Hesselbrock V, Hinrichs A, Kramer J, Kuperman S, Nurnberger JI Jr, Rice JP, Schuckit MA, Taylor R, Todd Webb B, Tischfield JA, Porjesz B, Foroud T. 2010. Genome-wide association study of alcohol dependence implicates a region on chromosome 11. Alcohol Clin Exp Res 34(5):840–852.

Elia J, Gai X, Xie HM, Perin JC, Geiger E, Glessner JT, D'arcy M, deBerardinis R, Frackelton E, Kim C, Lantieri F, Muganga BM, Wang L, Takeda T, Rappaport EF, Grant SF, Berrettini W, Devoto M, Shaikh TH, Hakonarson H, White PS. 2010. Rare structural variants found in attention-deficit hyperactivity disorder are preferentially associated with neurodevelopmental genes. Mol Psychiatry 15(6):637–646.

Epstein DJ, Vogan KJ, Trasler DG, Gros P. 1993. A mutation within intron 3 of the Pax-3 gene produces aberrantly spliced mRNA transcripts in the Splotch (Sp) mouse mutant. Proc Nat Acad Sci 90:532–536.

Ewald H, Flint T, Kruse TA, Mors O. 2002. A genome-wide scan shows significant linkage between bipolar disorder and chromosome 12q24.3 and suggestive linkage to chromosomes 1p22-21, 4p16, 6q14-22, 10q26 and 16p13.3. Mol Psychiatry 7(7):734–744.

Feng T, Zhu X. 2010. Genome-wide searching of rare genetic variants in WTCCC data. Hum Genet 128(3):269–280.

Fung HC, Scholz S, Matarin M, Simón-Sánchez J, Hernandez D, Britton A, Gibbs JR, Langefeld C, Stiegert ML, Schymick J, Okun MS, Mandel RJ, Fernandez HH, Foote KD, Rodríguez RL, Peckham E, De Vrieze FW, Gwinn-Hardy K, Hardy JA, Singleton A. 2006. Genome-wide genotyping in Parkinson's disease and neurologically normal controls: First stage analysis and public release of data. Lancet Neurol 5(11):911–916.

Furney SJ, Simmons A, Breen G, Pedroso I, Lunnon K, Proitsi P, Hodges A, Powell J, Wahlund LO, Kloszewska I, Mecocci P, Soininen H, Tsolaki M, Vellas B, Spenger C, Lathrop M, Shen L, Kim S, Saykin AJ, Weiner MW, Lovestone S. 2011. Alzheimer's Disease Neuroimaging Initiative. AddNeuroMed Consortium. Genome-wide association with MRI atrophy measures as a quantitative trait locus for Alzheimer's disease. Mol Psychiatry 16(11):1130–1138.

Ghezzi D, Arzuffi P, Zordan M, Da Re C, Lamperti C, Benna C, D'Adamo P, Diodato D, Costa R, Mariotti C, Uziel G, Smiderle C, Zeviani M. 2011. Mutations in TTC19 cause mitochondrial complex III deficiency and neurological impairment in humans and flies. Nat Genet 43(3): 259–263.

Gloriam DE, Schiöth HB, Fredriksson R. 2005. Nine new human Rhodopsin family G-protein coupled receptors: Identification, sequence characterisation and evolutionary relationship. Biochim Biophys Acta 1722(3):235–246.

Godlewska BR, Olajossy-Hilkesberger L, Limon J, Landowski J. 2010. Ser9Gly polymorphism of the *DRD3* gene is associated with worse premorbid social functioning and an earlier age of onset in female but not male schizophrenic patients. Psychiatry Res 177(1–2):266–267.

Gros-Louis F, Dupré N, Dion P, Fox MA, Laurent S, Verreault S, Sanes JR, Bouchard JP, Rouleau GA. 2007. Mutations in *SYNE1* lead to a newly discovered form of autosomal recessive cerebellar ataxia. Nat Genet 39(1):80–85.

Han MR, Schellenberg GD, Wang LS. 2010. Alzheimer's Disease Neuroimaging Initiative. Genome-wide association reveals genetic effects on human Aβ42 and τ protein levels in cerebrospinal fluids: A case control study. BMC Neurol 10:90.

Harris MJ, Gonyou HW. 2003. Savaging behaviour in domestic gilts: A study of seven commercial farms. Can J Anim Sci 83:435–444.

Hendriks-Stegeman BI, Augustijn KD, Bakker B, Holthuizen P, Van der Vliet PC, Jansen M. 2001. Combined pituitary hormone deficiency caused by compound heterozygosity for two novel mutations in the POU domain of the *Pit1*/*POU1F1* gene. J Clin Endocrinol Metab 86(4): 1545–1550.

Holt R, Barnby G, Maestrini E, Bacchelli E, Brocklebank D, Sousa I, Mulder EJ, Kantojärvi K, Järvelä I, Klauck SM, Poustka F, Bailey AJ, Monaco AP. 2010. EU Autism MOLGEN Consortium. Linkage and candidate gene studies of autism spectrum disorders in European populations. Eur J Hum Genet 18(9):1013–1019.

Jarvis S, McLean KA, Calvert SK, Deans LA, Chirnside J, Lawrence AB. 1999. The responsiveness of sows to their piglets in relation to the length of parturition and the involvement of endogenous opioids. Appl Anim Behav Sci 63:195–207.

Jarvis S, Reed BT, Lawrence AB, Calvert SK, Stevenson J. 2004. Per-natal environmental effects on maternal behaviour, pituitary and adrenal activation, and the progress of parturition in the primiparous sow. Anim Welfare 13:171–181.

Jones I, Craddock N. 2002. Do puerperal psychotic episodes identify a more familial subtype of bipolar disorder? Results of a family history study. Psychiatr Genet 12:177–180.

Jones I, Middle F, McCandless F, Coyle N, Robertson E, Brockington I, Lendon C, Craddock N. 2000. Molecular genetic studies of bipolar disorder and puerperal psychosis at two polymorphisms in the estrogen receptor alpha gene (*ESR1*). Am J Med Genet 96:850–853.

Jones I, Hamshere M, Nangle JM, Bennett P, Green E, Heron J, Segurado R, Lambert D, Holmans P, Corvin A, Owen M, Jones L, Gill M, Craddock N. 2007. Bipolar affective puerperal psychosis: Genome-wide significant evidence for linkage to chromosome 16. Am J Psychiatry 164(7): 1099–1104.

Joslyn G, Ravindranathan A, Brush G, Schuckit M, White RL. 2010. Human variation in alcohol response is influenced by variation in neuronal signaling genes. Alcohol Clin Exp Res 34(5):800–812.

Knap PW, Merks JWM. 1987. A note on the Genetics of Aggressiveness of Primiparous Sows Towards their Piglets. Livestock Prod Sci 17: 161–167.

Lee J-I, Tang Z-Z, Black DL. 2009. An inducible change in *Fox-1/A2BP1* splicing modulates the alternative splicing of downstream neuronal target exons. Genes Dev 23(19):2284–2293.

Lim J, Hao T, Shaw C, Patel AJ, Szabó G, Rual JF, Fisk CJ, Li N, Smolyar A, Hill DE, Barabási AL, Vidal M, Zoghbi HY. 2006. A protein–protein interaction network for human inherited ataxias and disorders of Purkinje cell degeneration. Cell 125(4):801–814.

Lin M, Pedrosa E, Shah A, Hrabovsky A, Maqbool S, Zheng D, Lachman HM. 2011. RNA-Seq of human neurons derived from iPS cells reveals candidate long non-coding RNAs involved in neurogenesis and neuropsychiatric disorders. PLoS ONE 6(9):e23356.

Liu Y, Blackwood DH, Caesar S, de Geus EJ, Farmer A, Ferreira MA, Ferrier IN, Fraser C, Gordon-Smith K, Green EK, Grozeva D, Gurling HM, Hamshere ML, Heutink P, Holmans PA, Hoogendijk WJ, Hottenga JJ, Jones L, Jones IR, Kirov G, Lin D, McGuffin P, Moskvina V, Nolen WA, Perlis RH, Posthuma D, Scolnick EM, Smit AB, Smit JH, Smoller JW, St Clair D, van Dyck R, Verhage M, Willemsen G, Young AH, Zandbelt T, Boomsma DI, Craddock N, O'Donovan MC, Owen MJ, Penninx BW, Purcell S, Sklar P, Sullivan PF. 2011. Wellcome Trust Case–Control Consortium. Meta-analysis of genome-wide association data of bipolar disorder and major depressive disorder. Mol Psychiatry 16(1):2–4.

Lydall GJ, Bass NJ, McQuillin A, Lawrence J, Anjorin A, Kandaswamy R, Pereira A, Guerrini I, Curtis D, Vine AE, Sklar P, Purcell SM, Gurling HM. 2011. Confirmation of prior evidence of genetic susceptibility to alcoholism in a genome-wide association study of comorbid alcoholism and bipolar disorder. Psychiatr Genet 21(6):294–306.

Maes M, Mihaylova I, Kubera M, Uytterhoeven M, Vrydags N, Bosmans E. 2009. Coenzyme Q10 deficiency in myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) is related to fatigue, autonomic and neurocognitive symptoms and is another risk factor explaining the early mortality in ME/CFS due to cardiovascular disorder. Neuro Endocrinol Lett 30(4):470–476.

Mahon PB, Payne JL, MacKinnon DF, Mondimore FM, Goes FS, Schweizer B, Jancic D. 2009. NIMH Genetics Initiative Bipolar Disorder Consortium; BiGS Consortium, Coryell WH, Holmans PA, Shi J, Knowles JA, Scheftner WA, Weissman MM, Levinson DF, DePaulo JR Jr, Zandi PP, Potash JB. Genome-wide linkage and follow-up association study of postpartum mood symptoms. Am J Psychiatry 166(11):1229–1237.

Mailman MD, Feolo M, Jin Y, Kimura M, Tryka K, Bagoutdinov R, Hao L, Kiang A, Paschall J, Phan L, Popova N, Pretel S, Ziyabari L, Lee M, Shao Y, Wang ZY, Sirotkin K, Ward M, Kholodov M, Zbicz K, Beck J, Kimelman M, Shevelev S, Preuss D, Yaschenko E, Graeff A, Ostell J, Sherry ST. 2007. The NCBI dbGaP database of genotypes and phenotypes. Nat Genet 39(10):1181–1186.

Marie S, Heron B, Bitoun P, Timmerman T, Van Den Berghe G, Vincent MF. 2004. AICA-ribosiduria: A novel, neurologically devastating inborn error of purine biosynthesis caused by mutation of ATIC. Am J Hum Genet 74(6):1276–1281.

Martin CL, Duvall JA, Ilkin Y, Simon JS, Arreaza MG, Wilkes K, Alvarez-Retuerto A, Whichello A, Powell CM, Rao K, Cook E, Geschwind DH. 2007. Cytogenetic and molecular characterization of *A2BP1/FOX1* as a candidate gene for autism. Am J Med Genet (Neuropsychiatr Genet) 144(7):869–876.

Novak G, LeBlanc M, Zai C, Shaikh S, Renou J, DeLuca V, Bulgin N, Kennedy JL, Le Foll B. 2010. Association of polymorphisms in the *BDNF*, *DRD1* and *DRD3* genes with tobacco smoking in schizophrenia. Ann Hum Genet 74(4):291–298.

Otowa T, Yoshida E, Sugaya N, Yasuda S, Nishimura Y, Inoue K, Tochigi M, Umekage T, Miyagawa T, Nishida N, Tokunaga K, Tanii H, Sasaki T, Kaiya H, Okazaki Y. 2009. Genome-wide association study of panic disorder in the Japanese population. J Hum Genet 54(2):122–126.

Percy MJ, Furlow PW, Lucas GS, Li X, Lappin TRJ, McMullin MF, Lee FS. 2008. A gain-of-function mutation in the *HIF2A* gene in familial erythrocytosis. New Eng J Med 358:162–168.

Potkin SG, Turner JA, Guffanti G, Lakatos A, Fallon JH, Nguyen DD, Mathalon D, Ford J, Lauriello J, Macciardi F. 2009. FBIRN. A genome-wide association study of schizophrenia using brain activation as a quantitative phenotype. Schizophr Bull 35(1):96–108.

Quilter CR, Blott SC, Wilson AE, Bagga MR, Sargent CA, Oliver GL, Southwood OI, Gilbert CL, Mileham A, Affara NA. 2007. Porcine maternal infanticide as a model for puerperal psychosis. Am J Med Genet (Neuropsychiatr Genet) 144(7):862–868.

Quilter CR, Gilbert CL, Oliver GL, Jafer O, Furlong RA, Blott SC, Wilson AE, Sargent CA, Mileham A, Affara NA. 2008. Gene expression profiling in porcine maternal infanticide: A model for puerperal psychosis. Am J Med Genet (Neuropsychiatr Genet) 147(7):1126–1137.

Ramos AM, Crooijmans RP, Affara NA, Amaral AJ, Archibald AL, Beever JE, Bendixen C, Churcher C, Clark R, Dehais P, Hansen MS, Hedegaard J, Hu ZL, Kerstens HH, Law AS, Megens HJ, Milan D, Nonneman DJ, Rohrer GA, Rothschild MF, Smith TP, Schnabel RD, Van Tassell CP, Taylor JF, Wiedmann RT, Schook LB, Groenen MA. 2009. Design of a high density SNP genotyping assay in the pig using SNPs identified and characterized by next generation sequencing technology. PLoS ONE. 4(8):e6524.

Renthal NE, Chen CC, Williams KC, Gerard RD, Prange-Kiel J, Mendelson CR. 2010. miR-200 family and targets, *ZEB1* and *ZEB2*, modulate uterine quiescence and contractility during pregnancy and labor. Proc Natl Acad Sci USA 107(48):20828–20833.

Schreiber E, Tobler A, Malipiero U, Schaffner W, Fontana A. 1993. cDNA cloning of human N-Oct3, a nervous-system specific POU domain transcription factor binding to the octamer DNA motif. Nucleic Acids Res 21(2):253–258.

Shen L, Kim S, Risacher SL, Nho K, Swaminathan S, West JD, Foroud T, Pankratz N, Moore JH, Sloan CD, Huentelman MJ, Craig DW, Dechairo BM, Potkin SG, Jack CR, Weiner MW Jr, Saykin AJ. 2010. Alzheimer's Disease Neuroimaging Initiative. Whole genome association study of brain-wide imaging phenotypes for identifying quantitative trait loci in MCI and AD: A study of the ADNI cohort. Neuroimage 53(3): 1051–1063.

Shibata H, Huynh DP, Pulst SM. 2000. A novel protein with RNA-binding motifs interacts with ataxin-2. Hum Mol Genet 9(9):1303–1313.

Stein JL, Hua X, Lee S, Ho AJ, Leow AD, Toga AW, Saykin AJ, Shen L, Foroud T, Pankratz N, Huentelman MJ, Craig DW, Gerber JD, Allen AN, Corneveaux JJ, Dechairo BM, Potkin SG, Weiner MW, Thompson P. 2010. Alzheimer's Disease Neuroimaging Initiative. Voxelwise genome-wide association study (vGWAS). Neuroimage 53(3):1160–1174.

Süsens U, Hermans-Borgmeyer I, Urny J, Schaller HC. 2006. Characterisation and differential expression of two very closely related G-protein-coupled receptors, *GPR139* and *GPR142*, in mouse tissue and during mouse development. Neuropharmacology 50(4):512–520.

Tassabehji M, Read AP, Newton VE, Harris R, Balling R, Gruss P, Strachan T. 1992. Waardenburg's syndrome patients have mutations in the human homologue of the Pax-3 paired box gene. Nature 355:635–636.

Uher R, Perroud N, Ng MY, Hauser J, Henigsberg N, Maier W, Mors O, Placentino A, Rietschel M, Souery D, Zagar T, Czerski PM, Jerman B, Larsen ER, Schulze TG, Zobel A, Cohen-Woods S, Pirlo K, Butler AW, Muglia P, Barnes MR, Lathrop M, Farmer A, Breen G, Aitchison KJ, Craig I, Lewis CM, McGuffin P. 2010. Genome-wide pharmacogenetics of antidepressant response in the GENDEP project. Am J Psychiatry 167(5):555–564.

Van den Oord EJ, Kuo PH, Hartmann AM, Webb BT, Möller HJ, Hettema JM, Giegling I, Bukszár J, Rujescu D. 2008. Genome wide association analysis followed by a replication study implicates a novel candidate gene for neuroticism. Arch Gen Psychiatry 65(9):1062–1071.

Van der Steen HAM, Schaeffer LR, de Jong H, de Groot PN. 1988. Aggressive behaviour of sows at parturition. J Anim Sci 66:271–279.

Van Winkel R. 2011. Genetic Risk and Outcome of Psychosis (GROUP) Investigators. Family-based analysis of genetic variation underlying psychosis-inducing effects of cannabis: Sibling analysis and proband follow-up. Arch Gen Psychiatry 68(2):148–157.

Vanti WB, Nguyen T, Cheng R, Lynch KR, George SR, O'Dowd BF. 2003. Novel human G-protein-coupled receptors. Biochem Biophys Res Commun 305(1):67–71.

Wei H, Malik M, Sheikh AM, Merz G, Ted Brown W, Li X. 2011. Abnormal cell properties and down-regulated FAK-Src complex signaling in B lymphoblasts of autistic subjects. Am J Pathol 179(1):66–74.

Wilkinson DG. 2001. Multiple roles of EPH receptors and ephrins in neural development. Nat Rev Neurosci 2(3):155–164.Review.

Williams NM, Zaharieva I, Martin A, Langley K, Mantripragada K, Fossdal R, Stefansson H, Stefansson K, Magnusson P, Gudmundsson OO, Gustafsson O, Holmans P, Owen MJ, O'Donovan M, Thapar A. 2010. Rare chromosomal deletions and duplications in attention-deficit hyperactivity disorder: A genome-wide analysis. Lancet 376(9750):1401–1408.