American Journal of Medical Genetics Part B (Neuropsychiatric Genetics) 144B:862–868 (2007)

Porcine Maternal Infanticide as a Model for Puerperal Psychosis

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Childbirth is a period of substantial rapid biological and psychological change and a wide range of psychotic disorders can occur ranging from mild 'baby blues' to severe episodes of psychotic illnesses. Puerperal psychosis is the most extreme form of postnatal psychosis, occurring in 1 in 1,000 births. In this study, we have used the pig as an animal model for human postnatal psychiatric illness. Our aim was to identify quantitative trait loci (QTL) associated with maternal (infanticide) sow aggression. This is defined by sows attacking and killing their own newborn offspring, within 24 hr of birth. An affected sib pair whole genome linkage analysis was carried out with 80 microsatellite markers covering the 18 porcine autosomes and the X chromosome, with the aim of identifying chromosomal regions responsible for this abnormal behavior. Analysis was carried out using the non-parametric linkage test of Whittemore and Halpern, as implemented in the Merlin software. The results identified 4 QTL mapping on *Sus scrofa* chromosomes 2 (SSC2), 10 (SSC10), and X (SSCX). The peak regions of these QTL are syntenic to HSA 5q14.3-15, 1q32, Xpter-Xp2.1, and Xq2.4-Xqter, respectively. Several potential candidate genes lie in these regions in addition to relevant abnormal behavioral QTL, found in humans and rodents.

KEY WORDS: puerperal psychosis; maternal infanticide; aggression; QTL linkage analysis; behavior

Please cite this article as follows: 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 Part B 144B: 862–868.

INTRODUCTION

Extreme behavior during and after pregnancy is sometimes seen in humans. Anxiety, which may be associated with episodes of panic and depression, occur in at least one-third of pregnant women. These are particularly prominent in women from the developing world perhaps because pregnancy is a time of high risk to the life and wellbeing of the mother [Cantwell and Cox, 2003]. Childbirth itself is a period of substantial rapid biological and psychological change and a wide range of psychotic disorders can occur ranging from mild 'baby blues' to severe episodes of psychotic illnesses [Jones et al., 2001].

'Baby blues' occurs in about 50% of women. Onset is around days 3–5 and includes symptoms of crying and depression, which only last for a few days. Post-natal depression on the other hand can last for a few months if untreated and occurs in 5–15% of women. Symptoms include depression, poor sleep and appetite, suicidal thoughts and self-blame [Jones et al., 2001]. Some women have obsessional thoughts and may even have true infanticidal feelings [Cantwell and Cox, 2003].

Puerperal psychosis however, is the most extreme form of postnatal psychosis, occurring in 1 in 1,000 births. Genetic factors are thought to play a role and family studies have shown that pregnant women with pre-existing bipolar disorder (also known as manic depression) have an increased risk of puerperal psychosis. Furthermore, family studies consistently demonstrate a difference in the risk of puerperal psychosis in individuals with a first degree relative with bipolar disorder and puerperal psychosis compared to those without [Jones and Craddock, 2001]. There is therefore some disagreement as to whether puerperal psychosis represents a condition in its own right or whether childbirth is a trigger to a variety of psychotic illnesses [Jones et al., 2001; Brockington, 2003]. It has been suggested that puerperal episodes identify a more familial subtype of bipolar disorder [Jones and Craddock, 2002].

Onset of puerperal psychosis is rapid, in the early postnatal period, usually within the first month, mania being common in the first 2 weeks after childbirth [Meltzer and Kumar, 1985; Cantwell and Cox, 2003]. Presentation is typically a rapid fluctuation of mood (manic and depressive symptoms), confusion and perplexity, in addition to symptoms of psychosis (delusions, hallucinations, marked behavioral disturbance). Thoughts of self-harm may be due to feelings of guilt, self-worthlessness, or hopelessness [Cantwell and Cox, 2003].

Due to the rapid onset of puerperal psychosis, at a time of great physiological change, it is thought that biological, probably hormonal mechanisms are likely to be the trigger for this condition. Evidence so far has shown that variation at the serotonin transporter gene (5-HTT), influences susceptibility of bipolar patients to puerperal psychosis [Coyle et al., 2000]. 5-HTT expression is influenced by oestrogen, the concentration of which falls dramatically at parturition [McQueen et al., 1997]. Rapid reduction in levels of oestrogen also reduces its antidopaminergic effect exposing

This article contains supplementary material, which may be viewed at the American Journal of Medical Genetics website at http://www.interscience.wiley.com/jpages/1552-4841/suppmat/index.html.

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Received 8 November 2006; Accepted 23 February 2007
DOI 10.1002/ajmg.b.30529

supersensitive dopamine receptors, which may also trigger psychosis [Wieck et al., 1991; Jones et al., 2000].

In pigs, maternal (infanticide) aggression has been estimated in large surveys of commercial pig farms to be 8% [Knap and Merks, 1987] and 7–12% [Van der Steen et al., 1988]. It has been suggested that optimum porcine behavior in the first day post partum is characterized by passivity, unresponsiveness to piglets and lateral lying to allow maximum access to teats [Jarvis et al., 1999]. However, sows prone to aggression may be restless [Ahlström et al., 2002; Chen et al., 2007, in submission] and usually attack and kill their newborn offspring within 24 hr of birth [Knap and Merks, 1987; Van der Steen et al., 1988] as part of an otherwise poorly characterized behavioral complex.

There are several factors that can affect porcine maternal behavior including genetic predisposition, the sows' previous experiences, current metabolic and endocrine status and local environmental factors. Infanticidal behavior may be predisposed in farm systems that confine sows at birth or otherwise thwart their natural behavior [Jarvis et al., 1999, 2004; Ahlström et al., 2002] but has not been definitely shown to occur more frequently in these systems compared to pasture-based systems through a controlled experiment. However, it has been shown that there is still considerable variation in maternal behavior in sows with equivalent metabolic status, which are housed in similar husbandry systems [Van der Steen et al., 1988; Fraser, 1990]. It has also been observed that the effect of different farms does not alter the incidence of aggression [Chen et al., 2007, in submission]. The variation is therefore due either to genetic predisposition or to the sows' previous experience. Aggressive infanticide has been seen more frequently in primiparous sows (gilts) than sows, suggesting that maternal experience is a factor [Van der Steen et al., 1988]. However, epidemiological analyses have clearly shown that aggressive infanticide has a strong heritable component, with daughter-dam heritability estimates reported to be as high as 0.4–0.9 [Knap and Merks, 1987] and 0.47–0.87 [Van der Steen et al., 1988]. This therefore suggests that a genetic predisposition to aggressive infanticide exists, that can be ameliorated by experience.

Maternal infanticide aggression in pigs has many features in common to a postnatal psychosis and it is our hypothesis that pigs can be used as a model for human postnatal illness, particularly puerperal psychosis. Table I summarizes the similarities between the two conditions. In this study, it was our goal to identify genomic regions with significant impact on maternal (infanticide) aggression in pigs and relate this to human psychiatric conditions, in relation to postnatal illness.

MATERIALS AND METHODS

Animals

The Pig Improvement Company (PIC) provided the animals used in this study. Aggressive animals were classified as sows, which killed at least one of their offspring by biting them to death, usually within 24 hr of birth. One hundred nineteen affected sib pairs (ASP), from 11 different lines (A–K), were identified as having executed this type of abnormal behavior. (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). Supplementary Table I shows the genetic background of each line and number of sibships. Pigs were housed under similar conditions in farrowing crates (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 within lines varied from 1.2% to 11.5%.

DNA Isolation

Genomic DNA was provided by PIC and extracted from porcine ear and tail tissue using commercial kits (Qiagen, UK).

Genotyping

Eighty microsatellite markers evenly spread across the genome (approximately 30 cM spacing) were selected based on their heterozygosity and ability to work in multiplexed polymerase chain reactions (PCRs). Markers were either chosen from Rohrer et al. [1997], or from previous microsatellite work by PIC involving several breeds. We estimated that eighty markers should be sufficient to detect quantitative trait loci (QTL) of medium to larger effects ($\geq$5% of genetic variance) using 119 affected sib pairs and that this should give us 80% power to detect QTL within 15 cM of a marker. Sequences for microsatellite primers were obtained from the following Internet sites, National Centre for Biotechnology Information (NCBI), UniSTS and http://www.animalgenome.org/pig/. Primers were labeled with fluorescent tags and we were able to design 18 multiplexed reactions to amplify 78 markers with each multiplex containing between 2 and 9 markers. In addition, 2 single primer PCRs were carried out and products pooled before analysis. A list of markers and their chromosome position is given in supplementary Table II. PCR products were resolved on an ABI3100 Genetic Analyser using Genotyper 3.5 software (Department of Genetics, University of Cambridge) and the resulting genotypes analyzed using GeneMapper software version 3.5.

Statistical Analysis

Affected sib pair linkage analysis was performed using the *npl* option of the Merlin software package [Abecasis et al., 2002]. Merlin implements the non-parametric linkage scores (NPL) of Whittemore and Halpern [1994] and the Kong and Cox [1997] LOD score. Non-parametric methods make no assumptions about the mode of inheritance or other

TABLE I. Maternal Infanticide in Pigs as a Model for Puerperal Psychosis

Puerperal psychosis	Maternal aggression in pigs
Affects 1/1,000 deliveries	Affects approx. 10% of animals in commercial herds—breed dependent
Subset of bipolar disorder	
Genetic and environmental components	Genetic and environmental components
Hormone levels important	Hormone levels thought to be important
Siblings at increased risk	Siblings at increased risk
See mother-daughter cases	See dam-daughter cases
Highest risk at first pregnancy	Highest risk at first pregnancy (gilts)
Early onset—within a month, mania common first 2 weeks	Early onset—within 24 hr
Anecdotal behavioral changes include restlessness and lack of sleep	Behavioral patterns show animals exhibit anxiety by being restless and show lack of passivity expected with normal mothering

parameters such as gene frequency. Although the methods are less powerful than parametric linkage analyses they have the advantage of being robust to errors. NPL has been shown to perform well, even in the presence of a complicated disease model [Barmada and O'Connell, 2001]. The implementation in Merlin uses multipoint estimation of identity by descent (IBD) status allowing genome regions in between markers to be scanned. Merlin also allows additional relationships between sib-pair families to be incorporated into the analysis, for example, some sib-pairs were linked by a common sire.

RESULTS

Maternal (Infanticide) Aggression QTL

Four QTL ($P < 0.05$), which affect maternal (infanticide) aggression in pigs were detected by the affected sib pair whole genome linkage analysis. Although after adjustment for multiple testing a P-value of 0.05 does not correspond to a genome-wide significance level of 5%, Lander and Kruglyak [1995] nevertheless recommend that it is worth reporting all regions with a nominal P-value of <0.05, encountered in a complete scan. One of these QTL (Xq) however, has a P value that is suggestive of linkage, on the scale of significance as defined by Lander and Kruglyak [1995] (LOD 2.21, $P = 0.0007$). Supplementary Table III summarizes the significance, range and peak of the 4 QTL with syntenic human chromosomal regions identified using the UNR comparative map and UIUC—alignment of pig linkage, RH and human maps (http://www.animalgenome.org).

The porcine X chromosome (SSCX) was found to be of particular interest in terms of maternal aggression. In fact the whole chromosome was found to be significant at the $P = 0.01$ level, which suggests that multiple loci along the X are contributing to the aggressive phenotype. When all breeds (LOD 2.21, $P = 0.0007$) were being considered the peak region of the QTL was located at Xq2.2 (87.5 cM; Fig. 1A). However, for the two lines with the greatest number of affected sibs, (C) Large White (LOD 1.21 $P = 0.009$) (Fig. 1B) and (D) Landrace/Duroc (LOD 1.173 $P = 0.002$; Fig. 1C), the peak region of the QTL was found at a more distal region at 102 cM, associated with marker SW1608, at Xq2.4. As this was the most distal marker used in our study the peak could in fact lie anywhere between 102 cM and Xqter. Samples were reanalyzed without these two breed lines and there appears to be a second QTL on Xp (LOD 0.71, $P = 0.04$; Fig. 1D). This QTL peak region is associated with marker SW2470 which maps to Xp2.1–2.2 (45 cM) but because no other Xp markers were used in the scan, this QTL could lie anywhere between Xpter and Xp2.1. The presence of two QTL at either end of the X chromosome would explain the slight shift in QTL position when all breeds were being considered.

The third QTL maps to SSC10 and was also significant across all breeds (LOD 1.16, $P = 0.01$; Fig. 2A). For line (C) Large White the significance was slightly lower (LOD 0.85, $P = 0.02$; Fig. 2B) but for line (D) Landrace/Duroc the significance was higher (LOD 1.87, $P = 0.005$; Fig. 2C).

The final and fourth QTL maps to SSC2 but was significant only in line (C) Large White (LOD 0.8, $P = 0.03$; Fig. 3). The predicted candidate genes, which lie close to the peaks of each QTL are summarized in supplementary Table IV.

Syntenic QTL

There is also evidence that QTL in syntenic chromosomal regions in humans and rodents to our porcine QTL, appear to control emotional states such as anxiety, obsessionality, panic, agoraphobia, alcoholism, fear, emotionality, and coping

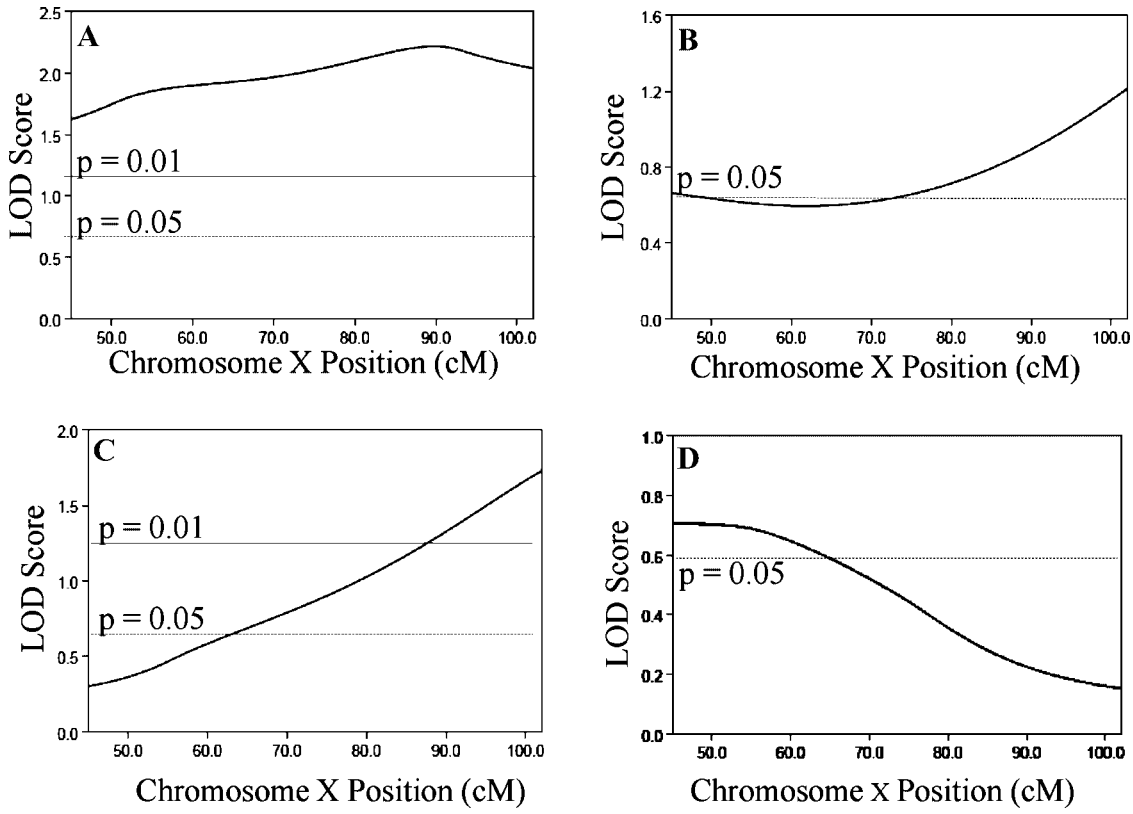

Fig. 1. SSCX QTL scans (**A**) All lines, (**B**) Line (C) Large white, (**C**) Line (D) Landrace/Duroc, (**D**) All lines except line (C) and line (D).

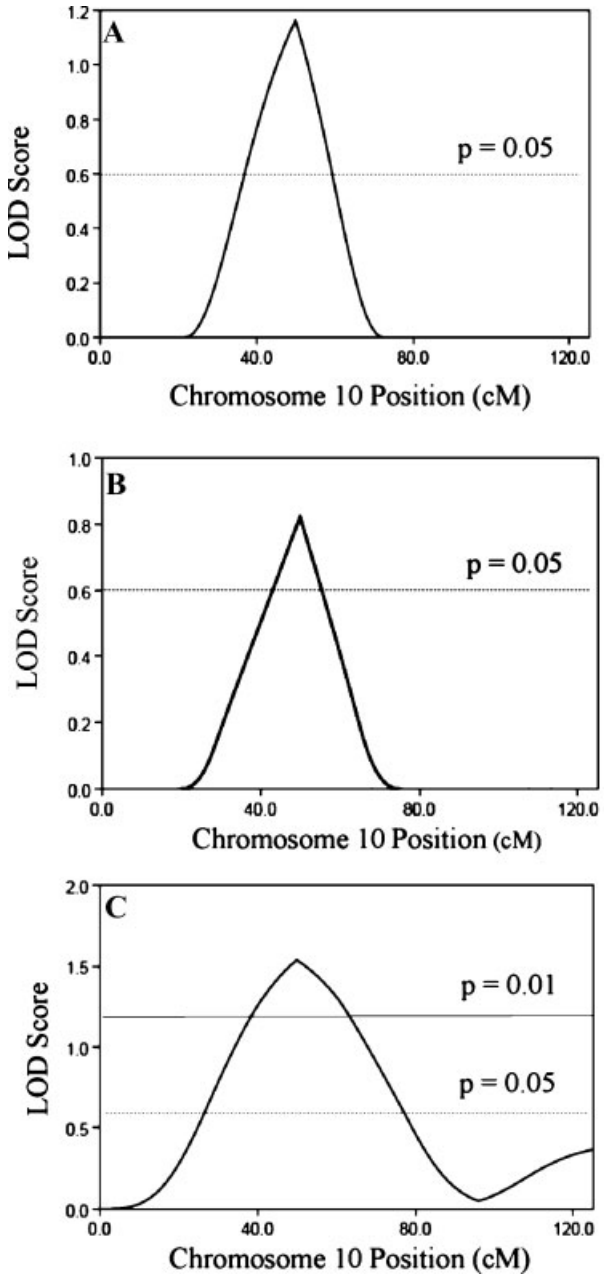

Fig. 2. SSC10 QTL scans (**A**) All lines, (**B**) Line (C) Large white, (**C**) Line (D) Landrace/Duroc.

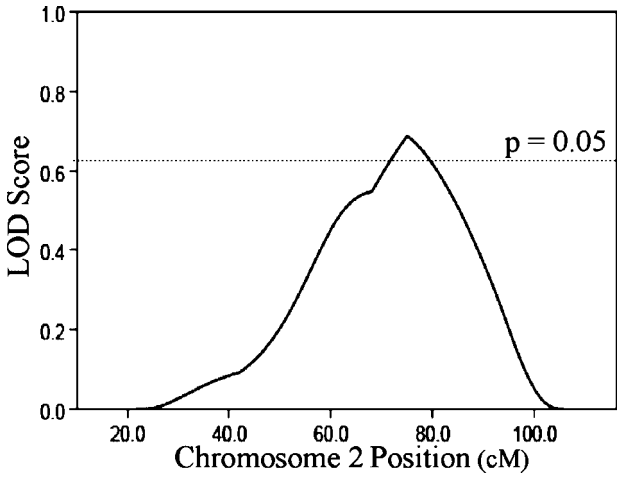

Fig. 3. SSC2 QTL scan Line (C) Large White.

behavior. This gives further credence to the fact that porcine infanticide aggression is a model for such abnormal behavior in humans. These syntenic QTL are summarized in Table II.

DISCUSSION

Four QTL, which affect maternal (infanticide) aggression in pigs were identified using a whole genome linkage analysis. We hypothesize that this abnormal porcine phenotype is a good model for puerperal psychosis, the most serious form of postnatal psychosis in humans. We discuss in more detail some of the predicted candidate genes, which are of particular relevance to an aggressive phenotype and lie close to the peaks of our QTL regions.

For the QTL on the short arm of the X chromosome, STS (steroid sulfatase) has been mapped to the pseudoautosomal region in pigs. The protein encoded by this gene catalyzes the conversion of sulfated steroid precursors to estrogens during pregnancy. STS is involved in neurosteroid biochemical pathways and neurosteroids are known to interact with neurotransmitters. In mice, aggressive behavior has been linked to this region [Roubertoux et al., 1994]. A genetic correlation has also been found between Sts concentrations in the liver in mice and aggressive behavior and Sts has been shown to modulate this aggressive behavior [Le Roy et al., 2000; Nicolas et al., 2001]. It was also found in mice that the QTL encompassing Sts interacted with other QTL such as those controlling first attack latency and number of attacks [Roubertoux et al., 2005].

For the long arm of the X chromosome, PGRMC1 (progesterone receptor membrane component 1) is a putative steroid membrane receptor, which has been mapped in the pig to

TABLE II. Behavior QTL in Syntenic Chromosome Regions

Behavioral disorder	SSC	HSA	References
Anxiety (anorexia)	10	1q31.1	Bacanu et al. [2005]
Obsessionality (anorexia)	10	1q31	Devlin et al. [2002]
PD/agoraphobia	10	1q31	Gelernter et al. [2001], Smoller et al. [2001]
Alcohol dependence	10	1q21-41	Buck et al. [2002]
Contextual fear	10	1q21-41	Caldarone et al. [1997]
Emotionality	10	1q21-41	Flint et al. [1995], Gershenfield et al. [1997], Rodriguez de Ledesma et al. [2005]
Coping behaviors	X	Distal X	Ahmadiyeh et al. [2003]
Alcohol dependence	2	5q14-21	Buck et al. [2002]
Anxiety	2	5q14.2-14.3	Kaabi et al. [2006]

Xq2.2 [Bertani et al., 2003]. It is interesting because homolog 25-Dx, found in the rat is similar in structure to cytokine and peptide hormone receptors, being most closely related to the prolactin receptor [Selmin et al., 1996]. It has been shown to bind several steroid hormones including progesterone (100%), testosterone (20%) and cortisol (4%) [Meyer et al., 1996]. In fact in the pig, high ratios of circulating estrogens to progesterone in late pregnancy have been associated with increased aggression towards their piglets [McLean et al., 1998] and progesterone receptor blockade during late pregnancy in mice leads to abhorrent maternal behavior including infanticide [Wang et al., 1995]. Twenty five-Dx is expressed in several brain regions, including hypothalamus known to regulate both feeding and reproductive behavior. 25-Dx is also co-expressed with vasopressin in the hypothalamus [Meffre et al., 2005]. Involvement of the vasopressin and serotonergic systems has been linked to the regulation of aggressive behavior, and differences in levels of expression of lysine vasopressin and serotonin receptor 1A (5HTR1A) have been detected in the brains of pre-pubertal female pigs [D'Eath et al., 2005].

Another gene, 5HTR2C (serotonin receptor 2C) maps to HSA Xq24 the human syntenic region of the porcine Xq QTL. 5HTR2C is a G-coupled receptor that stimulates phospholipase C (PLC) catalyzed hydrolysis of phosphatidylinositol bisphosphate, leading to mobilization of intracellular calcium and activation of protein kinase C. This is a very interesting candidate gene as it is linked to numerous abnormal behaviors. For example, serotonin regulates dopamine release via 5HTR2C and 5HTR3 receptors. Drugs that decrease 5HTR2C and increase 5HTR3 mediated dopamine release have been found to alleviate depression [Dremencov et al., 2006]. Increased 5HTR2C receptors may also be linked to alcoholism [Pandey et al., 1996] and decreased receptor activity is seen in suicide victims with a history of major depression [Gurevich et al., 2002]. Trifunovic and Reilly [2006] confirm the hypothesis that medial parabranchial nucleus neurones mediate anorexia through 5HTR2C receptors. Heisler et al. [2002] also found that 5-HT systems activate POMC (proopiomelanocortin) neurones and can be linked to anorexia. Furthermore, different isoforms of 5HTR2C mRNA are seen in Prader Willi patients compared to normal subjects. This is a genetic condition with many characteristics including mild to moderate mental retardation and behavioral problems including aggression [Kishore and Stamm, 2000]. In addition, other members of this gene family, namely 5HTR1A, 5HTR1B, and 5HTR2A have been associated with mood disorders and schizophrenia [Lopez-Figueroa et al., 2004]. Finally, variation in 5-HTT (neurotransmitter transporter, serotonin), which encodes an integral membrane protein that transports serotonin, has actually been associated with susceptibility to bipolar affective puerperal psychosis [Coyle et al., 2000].

For the QTL on SSC10, PTPRC (protein tyrosine phosphatase, receptor type, C), also known as CD45, maps to HSA 1q31 and has also been mapped to SSC10p. PTPs are signaling molecules that regulate a variety of cellular processes. PTPRC is an essential regulator of T and B cell antigen receptor signaling and also suppresses JAK kinases and regulates cytokine receptor signaling. This gene is a particularly good candidate as neuroinflammation, which may exacerbate neurodegeneration is found in conditions such as AD and Down syndrome, where behavior is strongly affected. It is thought that neuroinflammation may activate adhesion molecules such as CD45. The ERK and MAPK pathways are then activated which induce proinflammatory gene expression leading to the production of cytokines and chemokines [Hunter et al., 2004; Ho et al., 2005].

For the QTL on SSC2, a possible candidate gene is COX7C (cytochrome c subunit VIIc), which maps to the syntenic region HSA 15q14 (86 Mb). Cytochrome c is the terminal component of the mitochondrial respiratory chain and mitochondrial dysfunction has been associated with bipolar disorder and schizophrenia [Kato and Kato, 2000; Ben-Shachar, 2002]. Seelan and Grossman [1997] also showed that COX7C is the second nuclear gene of COX to be regulated by transcription factor YY1 and it is known that YY1 is a nuclear target for stress-related signaling pathways in neuronal degeneration [Korhonen et al., 1997]. In addition, cytochrome c deficiency in the muscle has also been associated with schizophrenic psychosis [Yamazaki et al., 1991].

These genes, or genes from pathways in which they are involved are likely candidates for maternal aggression and in turn puerperal psychosis. To add weight to these findings, a parallel microarray study looking at the difference in levels of gene expression in the hypothalamus of maternally aggressive pigs compared to matched controls, has also implicated some of these pathways, such as the MAP kinase and JAK/STAT, as pathways involved in the abnormal phenotype. In addition, differential expression of several genes, including G proteins, PRL (Prolactin), 5HTR2C, POMC, NMDA (N-methyl-D-aspartate), DRD2 (dopamine receptor 2), mitochondrial genes (including COX genes), a Prader Willi gene (necdin) and transcription factor YY1 was observed in our microarray study (Quilter et al., in preparation). Relevance of candidate genes in the QTL regions to microarray studies is also summarized in supplementary Table IV.

It was also seen that the significance of each QTL varied between breeds, with some QTL even being specific to certain breeds. This in itself is interesting as levels of aggression in animals are known to vary between breeds [Saetre et al., 2006]. Furthermore, it has also been observed that there is an increase in aggression in cross breeds. One possible explanation for this is that in such combinations, more contributing detrimental alleles have been brought together.

Psychiatric conditions are very complex with overlapping behavioral features. Puerperal psychosis itself also has a complex behavioral phenotype and it assumed that this is also the case for the maternal aggression seen in our pigs. It is interesting that different behavioral phenotypes have been found in syntenic chromosome regions to our peak regions, in other species. Anxiety and obsessionality QTL have been identified in syntenic chromosome regions in humans as covariates of anorexia. Eating disorders are examples of complex psychiatric phenotypes having both genetic and environmental influences. They span a substantial behavioral spectrum. Anorexia and Bulimia have been linked by psychometric studies to heritable personality and temperamental traits such as anxiety, obsessionality, perfectionism and harm avoidance [Klump et al., 2000; Bulik et al., 2003; Halmi et al., 2003; Fassino et al., 2004]. Anxiety and obsessional thoughts also commonly occur in human pregnancy in relation to health of the baby and anticipation of changes in lifestyle. In about one-third of women, anxiety is also associated with episodes of panic and obsessional thoughts are a symptom of post-natal depression [Cantwell and Cox, 2003]. Manifesting as periods of restlessness, anxiety may also be exhibited by maternally aggressive pigs although this has not been tested experimentally. In addition, family and genetic studies have consistently found that genes play a role in the etiology of panic disorder (PD) [Smoller and Tsuang, 1998; Smoller et al., 2001]. PD is characterized by recurrent panic attacks that include numerous symptoms (e.g., palpitations, fear of losing control) and often co-occurs with agoraphobia another anxiety disorder. A QTL for these behaviors has been identified in a syntenic human chromosome region [Gelernter et al., 2001]. QTL for alcohol dependence were also identified in syntenic chromosome regions in rodents, which is a condition often linked to depression [Buck et al., 2002]. A QTL for coping, or how one routinely deals with stress, was also identified in a syntenic

chromosome region in rodents, and is a complex behavioral trait with bearing on susceptibility to psychiatric disorders [Ahmadiyeh et al., 2003]. In relation to post-natal psychosis, depression is a major symptom and fear of inability to be able to cope with the care of a baby is typical, especially in first-time mothers [Cantwell and Cox, 2003].

Generally, it is thought that a number of fundamental mechanisms, from gene expression to hormonal release underlie the expression of emotional behavior in the mammalian brain. Therefore, although a gene or gene product may be a key component, all pathways that impact on its level via production, turnover and activity represent points of potential genetic variation that contribute to the observed behavioral phenotypes. Potentially, candidate genes from each QTL will be interlinked to result in the aggressive phenotype. We have already shown that more than one gene is involved in the MAP kinase and JAK/STAT pathways, which have also been identified as key pathways from our microarray studies (Quilter et al., in preparation). Further testing would be appropriate to refine our QTL by the identification of single nucleotide polymorphisms (SNPs) within or close to candidate genes along the length of the range of each QTL. These SNPs could be tested for an association with the aggressive phenotype seen in pigs. Any associations found could then be extended to patients with puerperal psychosis.

ACKNOWLEDGMENTS

This study was supported by a grant from The Department of the Environment, Fisheries and Rural Affairs (DEFRA). The authors would like to thank the Pig Improvement Company (PIC) for the provision of animal DNA samples, Rob Furlong for analysis of microarray data, Osman Jafer for microarray analysis and Chris Maddren, Department of Genetics, University of Cambridge for help with genotyping.

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