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# Loci associated with the chicken resistance to *Salmonella enteritidis* infection revealed by genome-wide association study

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**Abstract**

Salmonellosis is one of the most important foodborne diseases in the world. Salmonellosis caused by the *Salmonella Enteritidis* (SE) is an acute or chronic disease in chickens. To investigate host genetic resistance to *Salmonella enteritidis*, Genome-Wide Association Study (GWAS) was conducted on 40 SE-inoculated chickens based on a case control design, including 20 resistant and 20 susceptible chickens. The results showed that three SNPs were associated with host resistance to SE. One SNP of rs313281555 located in the LPP gene reached chromosome-wide significance (P<5.4e-07). Two suggestive SNPs, rs80757564 and rs313644723, were located in LRP5 and Wnt7b respectively. Moreover, genotype of those three loci was significantly associated with SE burden in cecal content (P<0.05). This is the first study to investigate SE-resistance loci, and paves the genetic basis for genetics of SE resistance in chicken.

**Keywords:** Chicken; Salmonella; Genome-wide association study

## Introduction

*Salmonella enteric* Serovar Enteritidis (SE) is a zoonotic enteric pathogen that is most frequently associated with diarrheal disease in humans while chickens serve as asymptotic carrier [1]. *Salmonella* outbreaks and subclinical infections are often the cause of economic, animal welfare costs and brought great danger to human health [2-7]. *Salmonella* infection was the most commonly reported food-borne illness of humans and has the largest number of hospitalizations and deaths in the United States each year [8].

Therefore, controlling *Salmonella* infection in poultry industry is important to reduce health risks for humans. Vaccination, antibiotics, and other drugs are most used to prevent SE infection. However, antibiotics can cause resistance of pathogens to antibiotic. Breeding for resistance to SE may be an alternative way to control salmonella in poultry. The disease resistant chickens can be selected at the phenotype level or genotype level [9]. Through candidate gene, microarray and next-generation sequencing technologies, many genes or loci have been identified to be associated with the resistance to *S. Enteritidis* in the past few years [10-16].

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Genome-wide association studies (GWAS) is one of the most effective methods to identify important SNPs and candidate genes associated specific trait. GWAS has been widely used to identify loci associated with milk production, birth weight, weight gain, susceptibility to *Mycobacterium avium ssp. paratuberculosis* tissue infection in cattle [17-19], host response to porcine reproductive and respiratory syndrome vaccination in nursery pigs [20], follicle number, body weight, resistance to Marek's disease in chicken [21-24]. The current study aimed to identify loci associated with SE resistance in chickens using GWAS.

## Materials and methods

### Animal trial and sample collection

JiningBairi, a China local chicken breed, was used in the current study. Two hundred 2-day old SE negative female chickens were orally inoculated with 0.3 ml of $5.8\times10^8$ cfu/ml SE (CVCC3377) in one batch. The inoculated chickens were raised in isolators with the same environment. Chickens were given *ad libitum* access to water and sterile feed. Chickens were sacrificed by cervical dislocation at 7 days post-inoculation (dpi). The cecal content was collected from each individual chicken and serially diluted for SE enumeration with bright green sulfadiazine Agar (Beijing Luqiao Technology Company). The cecum was collected and then stored at -80°C for DNA extraction. Animal experiment was approved by the Animal Care and Use Committee of Shandong Agricultural University (SDAUA-2014-015).

### Genome-wide association study

Forty chickens were selected for GWAS study based on the number of SE in cecal content. Twenty chickens with the lowest number of SE (resistant) and twenty ones with the highest number of SE (susceptible) were classified as resistant and susceptible group, respectively. Genome DNA was extracted from cecum using Tissue DNA Extraction Kit (Tiangen, Beijing, China). All samples were genotyped using the 600K Affymetrix Axiom Chicken Genotyping Array (Affymetrix Inc., Santa Clara, CA, USA).

Quality control and genotype calling were performed using Affymetrix Power Tools package according to the Axiom Genotyping Solution Data Analysis Guide (www.affymetrix.com). Samples with a dish quality control (DQC) value > 0.82 and call rate > 97% were used for further analysis. The QC metrics was generated by SNPolisher with the default parameters, and only SNPs that classified as PolyHighResolution, NoMinorHom, MonoHighResolution, Hemizygous, Off Target Variants were retained. In addition, 21,124 SNPs on sex chromosomes were removed since the current statistical methods are more powerful to detect the association between phenotypes and autosomal genotypes. The SNPs with minor allele frequency (MAF) <0.05 and Hardy-Weinberg equilibrium (HWE) test $P< 10^{-6}$ were discarded. A total of 39 samples (20 in resistant group and 19 in susceptible groups) and 384,966 SNPs distributed across 28 autosomes, LGE22 and LGE64 were used for further analysis (Table S1).

Association analysis was performed with PLINK [25] (Purcell et al. 2007) software using the standard Chi-square test. Bonferroni correction was used to adjust the multiple testing. Simple M [26] was used to estimate the number of independent tests. The genome-wide significant level ($P_{significant}$) is 0.05/N and the genome-wide suggestive level ($P_{suggestive}$) is 1/N, where N is the number of independent markers. A SNP was declared as significant if P-value <$P_{significant}$ or suggestive if P-value is less than $P_{suggestive}$ but greater than $P_{significant}$.

Two hundred samples were used for genotyping the significant or suggestive loci and association analysis. Genotype of each sample for each detected locus was recalled through LDR-PCR method. The specific primers were designed according to the flanking sequences of significant or suggestive SNPs (Table 1) using Primer 3 (http://frodo.wi.mit.edu/). The PCR was performed in 20 µL including 50 ng of genomic DNA, buffer 2 µL, 3 mM $MgCl_2$ 0.6 µL, 2mM deoxynucleoside triphosphate 2 ul, primers mix 2ul, and 0.2 Unit Taq DNA polymerase (Tiangen, Beijing, China). The PCR protocol consisted of an initial denaturation at 94°C for 2 min, 35 cycles of 30 s at 94°C, 56°C for 90 s, and 65°C for 30 s, followed by a final extension at 65°C for 10 min. The LDR PCR were performed using specific probes (Table 2) and in 10 ul reaction system of 4ul, buffer 1ul, probe mix 1ul, Taq DNA ligase 2U, $ddH_2O$ 4µL. The PCR condition was 94°C for 2 min, 40 cycles of 94°C for 15s, 50°C for 25s. Association between numbers of SE in cecal content with polymorphism of each of loci was analyzed through one way ANOVA using R package.

**Table S1:** Distribution of SNPs across chicken chromosomes

| Chromosome | Chromosome Length (bp) | Number of SNPs on array | Number of passed SNPs[a] | Averge distance (kb) |
|---|---|---|---|---|
| 1 | 195276750 | 102351 | 72174 | 2.71 |
| 2 | 148809762 | 64435 | 45226 | 3.29 |
| 3 | 110447801 | 57233 | 41526 | 2.66 |
| 4 | 90216835 | 43337 | 30853 | 2.92 |
| 5 | 59580361 | 30616 | 22247 | 2.68 |
| 6 | 34951654 | 21943 | 15611 | 2.24 |
| 7 | 36245040 | 21604 | 15977 | 2.27 |
| 8 | 28767244 | 17274 | 12553 | 2.29 |
| 9 | 23441680 | 18117 | 13273 | 1.77 |
| 10 | 19911089 | 18947 | 13178 | 1.51 |
| 11 | 19401079 | 13984 | 9551 | 2.03 |

| | | | | |
|---|---|---|---|---|
| 12 | 19897011 | 14829 | 10304 | 1.93 |
| 13 | 17760035 | 11282 | 7954 | 2.23 |
| 14 | 15161805 | 13181 | 9426 | 1.61 |
| 15 | 12656803 | 10505 | 7281 | 1.74 |
| 16 | 535270 | 584 | 260 | 2.06 |
| 17 | 10454150 | 9379 | 6603 | 1.58 |
| 18 | 11219875 | 9673 | 6585 | 1.70 |
| 19 | 9983394 | 9044 | 6201 | 1.61 |
| 20 | 14302601 | 9614 | 6683 | 2.14 |
| 21 | 6802778 | 8943 | 6044 | 1.13 |
| 22 | 4081097 | 4696 | 2865 | 1.42 |
| 23 | 5723239 | 6687 | 4406 | 1.30 |
| 24 | 6323281 | 7745 | 5359 | 1.18 |
| 25 | 2191139 | 2501 | 1587 | 1.38 |
| 26 | 5329985 | 6332 | 3936 | 1.35 |
| 27 | 5209285 | 5731 | 3605 | 1.45 |
| 28 | 4742627 | 5553 | 3537 | 1.34 |
| LGE22[b] | 965146 | 213 | 119 | 8.11 |
| LGE64[b] | 799899 | 89 | 42 | 19.05 |
| W | 1248174 | 14 | -- | -- |
| E[b] | 82363669 | 26642 | -- | -- |
| 0[c] | -- | 7883 | -- | -- |
| Total | 1040094497 | 580961 | 384966 | 2.7 |

a: SNPs passed the quality control and used for GWAS analysis, b: linkage groups, c: Those SNPs are not assigned to any chromosome.

### Genotyping and association study

**Table 1:** Primers used for the PCR

| SNP | Upper primer (5'-3') | Lower primer (5'-3') | Product length |
|---|---|---|---|
| rs313644723 | TCATTTTAATACGTTGCACCCTT | GCATCTTCCACCCTACAAGC | 332 |
| rs313281555 | GCATCTTCCACCCTACAAGC | GAAGTTTTACCTGGAGCCACA | 253 |
| rs80757564 | GAAGTTTTACCTGGAGCCACA | CTGCCATCAAACCCCATCAT | 189 |

**Table 2:** Probe sequence for each locus in LDR

| Probe name | Sequence (5'-3') | LDR length |
|---|---|---|
| **rs313644723_modify** | P-TAACTGTGTTCCTTACACGGTTTTTTTTTTTTTTTTT-FAM | |
| **rs313644723_C** | TTTTTTTTTTTTTTTTTTTGCCCCTCCTCACTCAGTCTG | 77 |
| **rs313644723_T** | TTTTTTTTTTTTTTTTTTTTGCCCCTCCTCACTCAGTCTA | 79 |
| **rs313281555_modify** | P-TCCAGAGCTTGAAATGTATCTTTTTTTTTTTTTTTTTTT-FAM | |
| **rs313281555_A** | TTTTTTTTTTTTTTTTTCAGCGTGAGCCCTCCAAACCTGT | 82 |
| **rs313281555_G** | TTTTTTTTTTTTTTTTTTTCAGCGTGAGCCCTCCAAACCTGC | 84 |
| **rs80757564R_modify** | P-TACTTGATTTTTGTTAACTTTTTTTTTTTTTTTTTTTTTTT-FAM | |
| **rs80757564R_A** | TTTTTTTTTTTTTTTTTTTTTCATGACCTGAGAATTGTGCTT | 87 |
| **rs80757564R_C** | TTTTTTTTTTTTTTTTTTTTTTTCATGACCTGAGAATTGTGCTG | 89 |

## Results

The average number of SE in resistant and susceptible groups was $6.25\times10^2$ and $1.78\times10^7$ cfu/g cecal content, respectively. The number of independent markers was 92,579. One significant and two suggestive SNPs were identified through GWAS mapping ($P_{significant}$<5.4e-07, $P_{suggestive}$< 1.08e-05) (Figure 1). The significant marker was rs313281555 (G/A) which was in intron 7 of *LPP* (LIM domain containing preferred translocation partner in lipoma) on GGA9 (*P*< 5.4e-07). Two suggestive markers were rs80757564 (G/T) and rs313644723 (T/C), which located in intron 10 of *LRP5* (LDL Receptor Related Protein 5) on GGA5 and the upstream of *WNT7B* on GGA1, respectively (*P*< 1.08e-05).

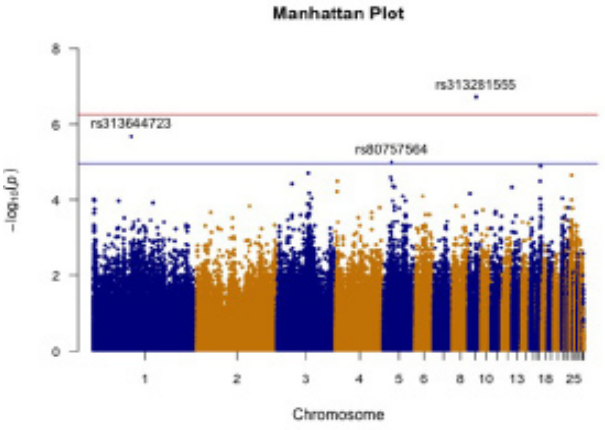


**Figure 1:** Manhattan plots showing association of all SNPs with SE in JiningBairi chickens.

*Note:* SNPs are plotted on the x-axis according to their position on each chromosome against association with these traits on the y-axis (shown as-log10 *p*-value). The blue line indicates suggestive genome-wise significance (*p*-value = 5.62E-05), and the red line shows genome-wise 5% significance with a p-value threshold of 2.81E-06.

Association of number of SE in cecal content with polymorphism of each of three loci was shown in Table 3. For the locus of rs80757564, the bacterial burden among chickens with different genotypes were significantly different (*P*<0.05), chickens with TT genotype had the highest bacterial burden in cecum content ($10^{8.50}$cfu/g), whereas chickens with GG genotype had the lowest bacterial burden of $10^{6.49}$cfu/g. For the locus of rs313281555, chickens with different genotypes had significantly different cecal bacterial burden *(P*<0.01), chickens with AA genotype had the highest bacterial burden of $10^{8.60}$cfu/g, chickens with GG genotype had the lowest bacterial burden of $10^{5.37}$cfu/g. For rs313644723 locus, chickens with TT had the highest bacterial burden of $10^{8.26}$cfu/g, chicken with CC genotype had the lowest bacterial burden of $10^{6.95}$cfu/g (*P*<0.05).

**Table 3:** The cecal bacterial burden of chickens with different genotypes of each locus

| SNPs ID | gene of candidate | Genotype | N | Cecal bacterial burden (logcfu/g) |
|---|---|---|---|---|
| rs80757564 (G/T) | LRP5 | TT | 70 | 8.50±0.24$^a$ |
| | | TG | 84 | 7.82±0.29$^a$ |
| | | GG | 29 | 6.49±0.64$^b$ |
| rs313281555 (A/G) | LPP | AA | 52 | 8.60±0.16$^A$ |
| | | AG | 97 | 8.27±0.20$^A$ |
| | | GG | 32 | 5.37±0.77$^B$ |
| rs313644723 (C/T) | Wnt7b | TT | 38 | 8.26±0.28$^a$ |
| | | CT | 94 | 8.24±0.21$^a$ |
| | | CC | 48 | 6.95±0.54$^b$ |

N: number of chickens. Different letters in the column mean significant difference, uppercase means *P*<0.01, lowercase means *P*< 0.05.

## Discussion

SNP of rs313644723 (*Wnt7b*) was located at 71 Mbp on chicken chromosome 1 (GGA1). There was a Salmonella-resistant QTL located at 53.1-79.3 Mbp on GGA1 (http://www.animalgenome.org/) [27]. The candidate gene Wnt7b belongs to the Wnt signaling pathway, which is closely related to the development and differentiation of cells, and plays an important role in normal and tumor cell growth and development [28, 29]. The SNP of rs80757564 (*LRP5*) was significantly associated with carcass weight and bone marrow weight [30]. *LRP5* acts as a cell membrane receptor of the Wnt signaling pathway, which plays an important role in the Wnt signaling pathway [31]. Both rs313644723 (Wnt7b) and rs80757564 (*LRP5*) were suggestively associated with SE burden in the current study. For rs313644723 marker, chickens with CC genotypes had lower bacterial burden than chickens with TT and CT genotypes. For rs80757564, chickens with GG genotypes had lower cecal bacterial burden than chickens with other genotypes, and had the highest expression level than other genotypes. All of these results add the evidence that both Wnt7b and LRP5 play important role in the response to SE inoculation.

LPP (Lipoma Preferred Partner) is a zyxin-related cell adhesion protein [32] and plays pivotal roles in cytoskeletal organization, organ development and oncogenesis [33]. It has been reported that *LPP* is associated with childhood obesity [34], vitiligo TA [35], cytokine response in smallpox vaccine recipients [24], polycystic ovary syndrome [36], celiac disease [37] and follicular lymphoma [38]. LPP is the substrate of protein-tyrosine-phosphatase1B (PTP1B) [39]. PTP plays an important role in the occurrence of IR as a negative regulator in the insulin pathway [40]. LPP localizes in focal adhesions, which are sites of membrane attachment to the extracellular matrix, and in cell–cell contacts [41]. It has reported that focal adhesion pathway is significantly enriched following SE inoculation [15]. The locus of rs313281555 (LPP) is associated with SE burden in the current study. Chickens with GG genotypes had lower cecal bacterial burden than other genotypes. This indicated that LPP is involved in the response to SE inoculation.

## Conclusion

In the current study, we conducted a GWAS in SE susceptible and resistant JiningBairi chickens by the 600K high density chip for the first time. Three loci, rs313281555 (A/G), rs313644723 (C/T) and rs80757564 (G/T) contribute to the *Salmonella enteritidis* resistance in chicken.

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