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Sex Difference in the Expression and Gene Network of Epidermal Growth Factor Receptor in Pituitary Gland in Mice

Yuhan Chen[1]*, Chuanming Liu[2]*, Qingyi Liu[3], Fengxia Liu[3,4],Yan Jiao[4], Hassan Almoazen[5], Jiaqian Zhu[6], Weikuan Gu[4#], Helin Feng[3,4#]

[1]Guang'anmen Hospital, China Academy of Chinese Medical Sciences, Beijing, China
[2]Shijiazhuang No 1 High School, Shijiazhuang, Hebei, China
[3]The Fourth Hospital, Hebei Medical University, Shijiazhuang, Hebei, China
[4]Department of Orthopaedic Surgery, Campbell Clinic and Pathology, University of Tennessee Health Science Center, Memphis, USA
[5]Department of Pharmaceutical Sciences, University of Tennessee Health Sciences Center, 881 Madison Ave, Memphis, Tennessee, USA
[6]Department of Biological Science, Rust College, Holly Springs, Mississippi, USA

Abstract

Background: Epidermal growth factor receptor (EGFR) involves in diverse cellular functions and plays an important role in the pathogenesis of many malignancies in the human population. The pituitary gland is a target of epidermal growth factor (EGF) and it is well known that EGFR plays a role in pituitary tumor as well as other tumors formation and progression.

Methods: In this study, we have screened expression profiles for the whole genome of pituitary genes of both sexes from multiple mouse recombinant inbred strains. In addition, using Network Graph, we have constructed the gene network in combination with the correlation matrix. To determine the chromosomal locations that regulate the expression of Egfr in females and males, the transcriptome mapping was conducted using Gene Network mapping tool. Furthermore, we conducted bioinformatics analysis to identify genes that have been reported to regulate or functionally connect to Egfr.

Results: Statistical analysis of Egfr expression levels between female and male mice produced a P value of 1.56442E-09. The R value obtained from the correlation analysis is 0.22. A considerable number of genes in the gene network of Egfr showed sex difference. These genes are known important in caner pathways. The eQTLs that regulate the expression levels of Egfr also showed sex difference. Gender difference of the correlations between Egfr expression levels and the T cell growth is also observed.

Conclusion: Our data suggest that sex difference in the expression levels of Egfr may have a significant impact on immunological disorders.

Keywords: Egfr; eQTL; Gene network; Expression; Mouse; Pathway; Pituitary; Sex

Abbreviations

Akt1: Thymoma Viral Proto-Oncogene 1; AXL: AXL Receptor Tyrosine Kinase; Cntln: Centrosomal Protein; eQT: Expression Quantitative Trait Loci; Egf: Epidermal Growth Factor; Egfr: Epidermal Growth Factor Receptor; Fech: Errochelatase; Gas6: Growth Arrest Specific; Qrb2: Growth Factor Receptor Bound Protein 2; Klrb1: Killer Cell Lectin-like Receptor Subfamily B Member 1A; Mtor: Mechanistic Target of Rapamycin; Mapk1: Mitogen-Activated Protein Kinase 1; Nrcam: Neuron-Glia-CAM-related Cell Adhesion Molecule; Pi3k: Phosphatidylinositol 3'-Kinase; PSA: Prostate-specific Antigen; Raf1: v-raf-Leukemia Viral Oncogene 1; RI: Recombinant Inbred; Sos1 (2): Son of Seven Less Homolog 1 (sos1); 2; Tgfa: Transforming Growth Factor Alpha

Introduction

Background

The pituitary gland is found in all vertebrates. It secretes hormones that control variety of metabolic processes and organ functions including growth, blood pressure, and certain functions of the sex organs. Pituitary tumor affects the normal hormone-releasing cells of the pituitary therefore it causes the lack of or unbalanced hormone releasing from pituitary gland [1].

Epidermal growth factor receptor (EGFR) is involved in diverse cellular functions and plays an important role in the biological and pathogenesis of pituitary gland [2]. Its expression in pituitary tumors has been known since as early as in 1994 [3,4]. Its values in pathological and prognosis in several pituitary related cancers, including pituitary macroadenomas and glioblastoma, have been studied [5]. Very recently, EGFR has been recognized as promising targets for treating adrenocorticotropic hormone (ACTH)-producing pituitary adenomas (ACTHomas) such as Cushing's disease [6].

Accordingly, EGFR is a rational target for cancer therapy for pituitary tumor and variety of cancers. Several drugs targeting EGFR have been involved in therapeutic applications while others are in clinic trials. At the same time, multiple mutations in the EGFR gene have been identified as a major cause for the failure of Erlotinib and Gefitinib in the treatment of patients harboring non-small-cell lung cancer (NSCLC) who initially responded to this therapy [7]. Polymorphism differences of EGFR among ethnic/racial groups has been documented [8]. It has been suggested that these differences may potentially influence the differential response to ramucirumab [8].

It has been known that the frequency of pituitary adenomas varies greatly according to the sex. In a retrospective review of the records of 2230 patients who underwent surgery for a pituitary adenoma,

***Corresponding author:** Weikuan Gu, Guang'anmen Hospital, China Academy of Chinese Medical Sciences, Beijing, China, Tel: 1-901-448-2259; E-mail: wgu@uthsc.edu

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Mindermann and Wilson found that the various adenoma types have their peak occurrence in distinctly different age groups and differ greatly in their female-to-male ratios [9].Variety of studies have reported the gender-related differences in disease phenotypes and treatment outcomes in patients who are surgically treated and histologically proven pituitary adenomas [10,11]. Furthermore, recently Olsson et al reported that women with nonfunctioning pituitary adenomas (NFPA) have a higher incidence of comorbidities than men with NFPA [12].

Tremendous progress has been made on the study of sex difference in biological function of disease related genes [13]. It has been realized that precision medicine will not be achieved without understanding of the sex difference [13]. For example, there are considerable reports on the gender associated gene expression that are important to survival of cancer [14]. EGFR polymorphisms has been linked to the gender-related survival in metastatic colon cancer [15]. The differential over expression of EGFR in cancers of men and in women have also been reported [16]. Earlier, the increased copy number of EGFR has been linked to the poor prognosis in head and neck squamous cell carcinomas [17]. Because EGFR is produced by pituitary gland, obviously its expression level is different between men and women over the life time. However, the gender difference in molecular pathways and regulation of EGFR remain elusive.

Due to the difficulties in using human populations, animal models, especially the mouse models have been widely used for the studies of sex difference. The advantage of using animal model is that the study can be done with multiple individuals from the same homozygous mouse strain [18]. Multiple mice can be obtained from the same strains with the same genomic background but different at sex. All animals can be bred and kept in the same animal facility with the same environment. In recent years, the recombinant inbred (RI) strains derived from C57BL/6J (B6) X DBA/2J (D2) have been widely applied for the study of sex differences [19,20]. The BXD strain set is the largest mouse RI panel [21].

In the present study, we systematically investigated the sex differences of EGFR in pituitary gland using high quality data from BXD RI population.

Materials and Methods

Data on expression levels of Egfr

To select genes that are known in the molecular pathways of the EGFR axis and compare their expression levels between females and males, we used a dataset generated from the mouse pituitary gland at GeneNetwork (http://www.genenetwork.org/webqtl/main.py?FormID=sharinginfo&GN_AccessionId=427) [19]. The name of the dataset is INIA Pituitary Affy MoGene 1.0 ST (Jun12): It includes gene expression data for the whole pituitary across 42 strains of mice of both sexes from BXD. Microarray data was generated by using GeneChip® Mouse Gene 1.0 ST Array. Data posted on the webpage were treated by conventional Affymetrix gene level probe summarization (RMA) followed by log2 transformation and standard GeneNetwork variance stabilization (2z+8). The z scores are multiplied by 2 and we then add a value of 8 to all values (http://www.genenetwork.org/webqtl/main.py?FormID=sharinginfo&GN_AccessionId=428).

Collections of data on expression levels of Egfr and associated genes

For the expression data of Egfr and its associated genes we collected the expression data of Egfr axis in pituitary from the male and the female mice. We used the Actin beta as controls for the Egfr. When multiple probes are presented for the gene, the probe with the highest expression level was chosen for the analysis while the others were used as reference.

Gene network construction

The gene network was constructed using tools in GeneNetwork. We constructed the gene network based on the Network Graph in combination with the Correlation Matrix. Procedure followed our previously studies [18-20]. For each sex in each pair of samples, both the Network Graph and Correlation Matrix were obtained with the same set of parameters or criteria. For example, for the Line Threshold in the Network Graph, absolute values greater than 0.35 will be used across all samples. The Spring Model layout (force reduction) was used for the graphic method for all graphic samples.

Mapping the transcriptomic loci (eQTL) that regulates the expression level of Egfr in female and male mice

Transcriptome mapping with GeneNetwork was conducted to identify the chromosomal regions that affect the expression of Egfr in female and male. After we obtained the transcriptome maps, we compared them to see whether there is a difference between maps of female and male mice and among different tissues. We have focused on the loci that have LOD score equal to or higher than the significant levels [21]. For the loci showing sex difference, we have examined the candidate genes that regulate the Egfr expression level. We have focused on the genes under the peak region of the eQTL, which usually is the chromosome region with LOD scores at significant or suggestive levels [21]. After we identified the genes in the chromosome region under the peak region of eQTL, we conducted bioinformatics analysis to examine whether any of these genes have been reported to regulate or functionally connect to Egfr. We employed the PGMapper to conduct such a search [22]. It is a software tool for automatically matching defined functional terms to genes from a defined genome region by combining the mapping information from the Ensemble database and gene function information from the OMIM and PubMed databases.

Statistical analysis

The top 50 associated genes in each dataset on the basis of Pearson correlation were used for plotting Network Graphs in GeneNetwork. T–test was perfumed to test the levels of gene expression levels between male and female mice. P value of 0.05 was regarded as the largest value of indication of significant difference of the two populations.

Results

Expression level of Egfr between female and male in pituitary gland

We conducted statistical analysis using data of gene expression of pituitary gland from a total of 42 strains, which have both the data from Actin B and Egfr in both sexes. There is one probe for Actin B on the INIA Pituitary Affy MoGene 1.0 ST chip. The expression levels of Actin B in female and male mice of different strains (Figures 1A and 1B). For Actin B, the P value for T test between female and male is 0.55. The R value from the correlation analysis is -0.07. These data indicated that there is no difference in the expression levels of Actin between male and female mice.

Similarly, we obtained one probe for Egfr on the UNC INIA Pituitary Affy MoGene 1.0 ST chip in the expression levels of Egfr in female and male mice of different strains (Figures 2A and 2B). We also

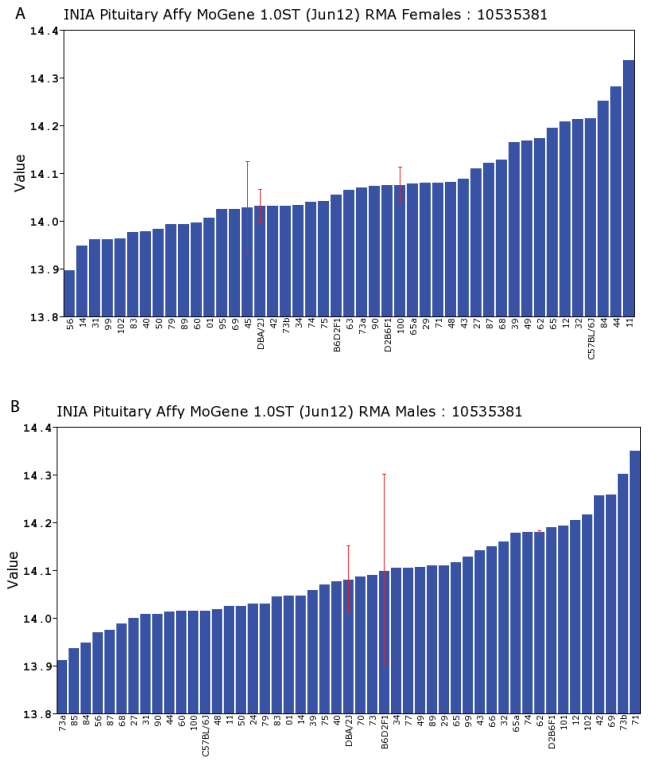

Figure 1: Expression levels of Actin B in pituitary gland between female and male mice in BXD strains. Numbers on left vertical are for the relative levels of expression of Actin B. The information of strains and names of standard inbred strains are listed under the horizontal axis. Red Bars indicate significant variation existing among the mice of that strain. **1A:** The expression levels of Actin B in pituitary gland of female mice. **1B:** The expression levels of Actin B in pituitary gland of male mice.

conducted the same statistical analyses on the levels of Egfr expression between male and female mice. For Egfr, the P value for T test between female and male is 1.56442E-09. The R value from the correlation analysis is 0.22. Therefore, there seems a difference in the expression levels between male and female mice. Thus, there is no difference in the expression level of Actin B between female and male populations while there is a significant sex difference in the Egfr expression levels. Therefore, further analyses were conducted as shown in the next several sections.

Gene network of Egfr between female and male in moue pituitary gland

Using the data on the expression level of probe ID, 10374366, the probe for Egfr and whole genome expression profiles in the pituitary glands of RI strains, we identified the top 50 probes of genes with their expression levels mostly correlated to that of Egfr. The correlation matrix of these 50 genes is constructed (Supplementary Table S1).

Egfr is positively and negatively to several genes (Figure 3A). The expression of mouse Egfr is strongly positively correlated to probe BC067074 which is positively associated to centlein, centrosomal protein (Cntln). Cntln in turn positively associated with several other genes including ferrochelatase (Fech) and neuron-glia-CAM-related cell adhesion molecule (Nrcam).

We then constructed a gene network using the same probes from female gene expression profiles of pituitary gland. As shown in Figure 3B, although many of genes showed similar connections between male and female mice, Egfr in female does not have as much influence on the expressions of these genes as that in male. In addition, Egfr does not have a stronger connection to probe BC067074 in female. It has no significant influence on the expression levels of Cntln, Fech and Nrcam.

The expression levels of genes most differently associate to Egfr between female and male in mouse pituitary gland. Based on these difference, we constructed matrix of gene interaction. We further examined the correlation in detail between the expression level of Egfr and several genes in male and in female mice. The expression levels between more than half of these genes and Egfr showed similar correlations in male and female mice. For example, in both male and female mice, the expression levels of Egfr are positively correlated to that of LIM domain only 4 (Lmo4) (Figures 4A and 4B). However, the expression level of some genes and Egfr showed different correlations between male and female mice. Specifically, in male, the expression levels of Egfr is strongly positively connected to the expression levels of growth arrest specific 6 (Gas6) and neuron-glia-CAM-related cell adhesion molecule (Nrcam) among the RI strains, while in female there is no such a strong connection (Data not shown) (Figures 4C and 4D). In male, the expression level of Egfr is strongly negatively connected to the expression of killer cell lectin-like receptor subfamily B member 1A (Klrb1a) while in female there is no such a connection (Figures 4E and 4F). These data confirm a significant difference in the Egfr pathways between male and female mice in pituitary gland.

The expression levels of genes known in the Egfr pathways between female and male in moue pituitary gland. Next, we examined the

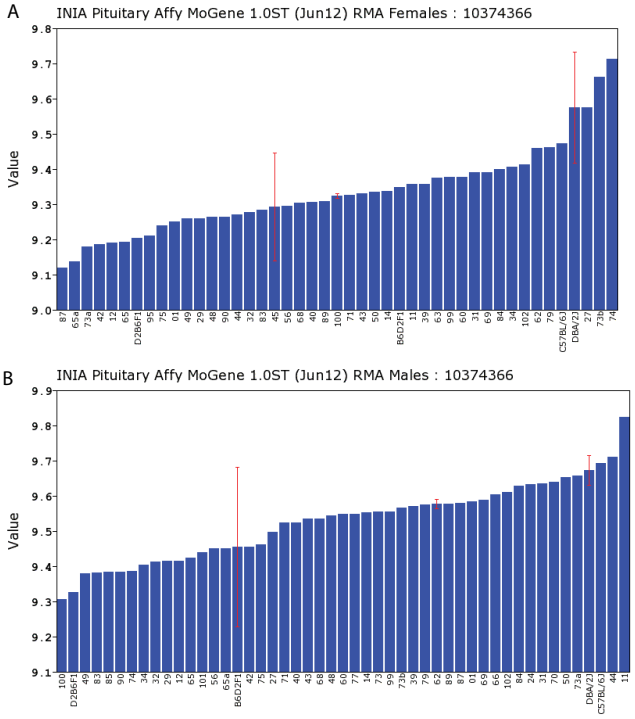

Figure 2: Expression levels of Egfr in pituitary gland between female and male mice in BXD strains. Numbers on left vertical are for the relative levels of expression of Egfr. The information of strains and names of standard inbred strains are listed under the horizontal axis. Red Bars indicate significant variation existing among the mice of that strain. **2A:** The expression levels of Egfr in pituitary gland of female mice. **2B:** The expression levels of Egfr in pituitary gland of male mice.

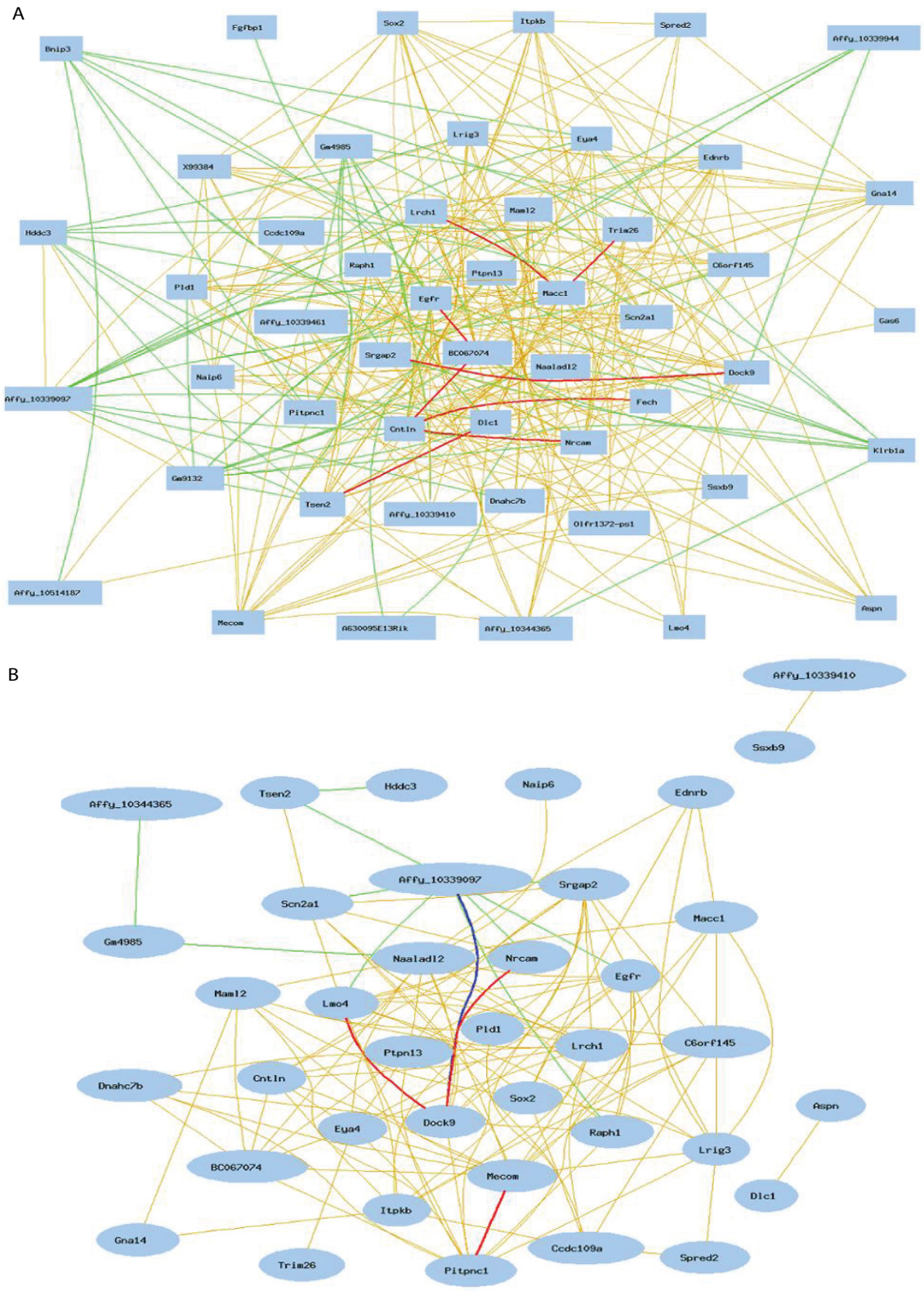

Figure 3: Gene network in pituitary gland. The 50 nodes in the graph below show the selected traits. Only nodes with edges are displayed. The graph's canvas is 40.0 by 40.0 cm and the node labels are drawn with a 16.0 point font and the edge labels are drawn with a 14.0 point font Colors of lines represent different R values. Red=0.7-1, Pink=0.5-0.7, grey pink=0-0.5, Black=-0.5-0, Green=-0.7- -0.5, Blue=-1- -0.7. **3A:** Gene network of top 50 genes that closely associated to Egfr in male mouse Pituitary gland. The 390 edges between the nodes, filtered from the 1225 total edges and drawn as curves, show Pearson correlation coefficients greater than 0.5 or less than -0.5. **3B:** Gene network of top 50 male genes that closely associated to Egfr in female mouse Pituitary gland. The 124 edges between the nodes, filtered from the 1225 total edges and drawn as curves, show Pearson correlation coefficients greater than 0.5 or less than -0.5.

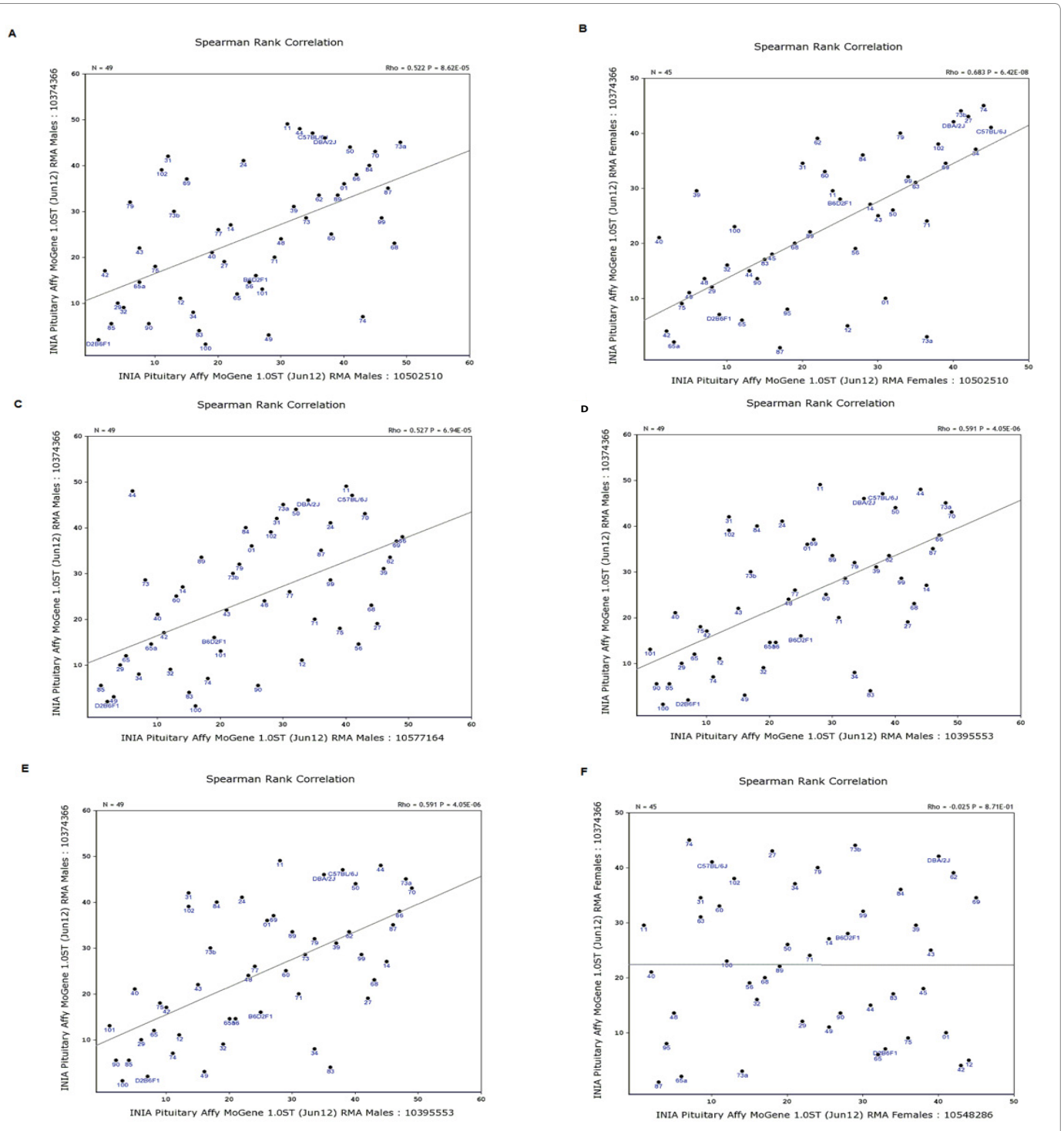

Figure 4: Correlations between the expression level of Egfr and four other genes. The expression levels of Egfr are positively correlated to that of Lmo4 in male mice. The expression levels of Egfr are positively correlated to that of Lmo4 in female mice. The expression levels of Egfr is strongly positive.

genes that are well-known in the pathways of Egfr. These genes include thymoma viral proto-oncogene 1 (akt1), Epidermal Growth Factor (Egf), growth factor receptor bound protein 2 (grb2), mechanistic target of rapamycin (mtor), mitogen-activated protein kinase 1 (Mapk1), v-raf-leukemia viral oncogene 1 (raf1), Son of seven less homolog 1 (sos1), sos2, and transforming growth factor alpha (Tgfa). These genes are important in the known Egfr pathway [21,23-26]. It is well known in humans that (EGF) binds to EGF Receptor. EGF and EGFR) lead to activation of downstream kinases including phosphatidylinositol 3'-kinase (PI3K), Akt, mtor [21]. AKT facilitates EGFR trafficking and degradation by phosphorylating and activating PIKfyve [23]. Grb2 plays important role in EGF-stimulated EGFR internalization [18]. It is known that Tgfa expression drives constitutive epidermal growth factor receptor pathway activation and sensitivity to gefitinib [24].

Based on the expression level, we constructed the gene network of these genes between male and female (Figures 5A and 5B). While most of their connections between male and female mice are similar, there is one difference. In male mice, there is no association in expression between Egf and Egfr (Figure 5C). The R value between expression level of Egf and Egfr is -0.182, with a P value of 0.213. However, in female, there is positive correlation, with P value of 0.029 (Figure 5D). Thus, in one hand, these data indicate the reliability of the data because of the confirmation of connected pathway among these genes; on the other hand, the data also reveal the existing of sex difference.

Gene regulation of the expression of Egfr in female and male pituitary gland

We finally examined the genetic factors that regulate the expression of Egfr in pituitary gland of female and male mice. With 5000 permutation test, we did not detect strong eQTLs for the regulation of Egfr from either female or male mice (Figure 6A). We obtained an eQTL on chromosome 2 from female mice. The eQTL is at the suggestive level with the peak area between 61.5 and 65.0 Mb (Figure 6B). This region contains 13 genetic elements. From the male, an eQTL was detected on chromosome 17, with the peak region between 27.5 to 30 Mb. This region contains a total of 71 genetic elements. However, we did not find any genetic elements which the expression level is highly correlated to that of Egfr from the gene expression data of either female or male mice. The QTL mapping suggests that the expression levels of Egfr are differently regulated in male and female mice.

The expression level of Egfr and immune traits in female and male mice

Egfr has a broad impact on the development and immunology. We examined the potential effect of the expression of Egfr on the T cell between female and male mice. We used the data of early investigation on the T cell growth for the correlation analysis. A few number of BXD stains were used for the analysis of Genetic linkage of thymic T-cell proliferative unresponsiveness [24]. Our analysis indicated that the expression levels of Egfr in both sexes have positive correlations with the Thymic T-cell proliferative unresponsiveness (anergy) to anti-CD3-induced proliferation (chemokine-associated) (Figures 7A and 7B). Thus, in this case, the expression levels of both sexes have the same immunological impact. Previously, Jenkins et al. have isolated and

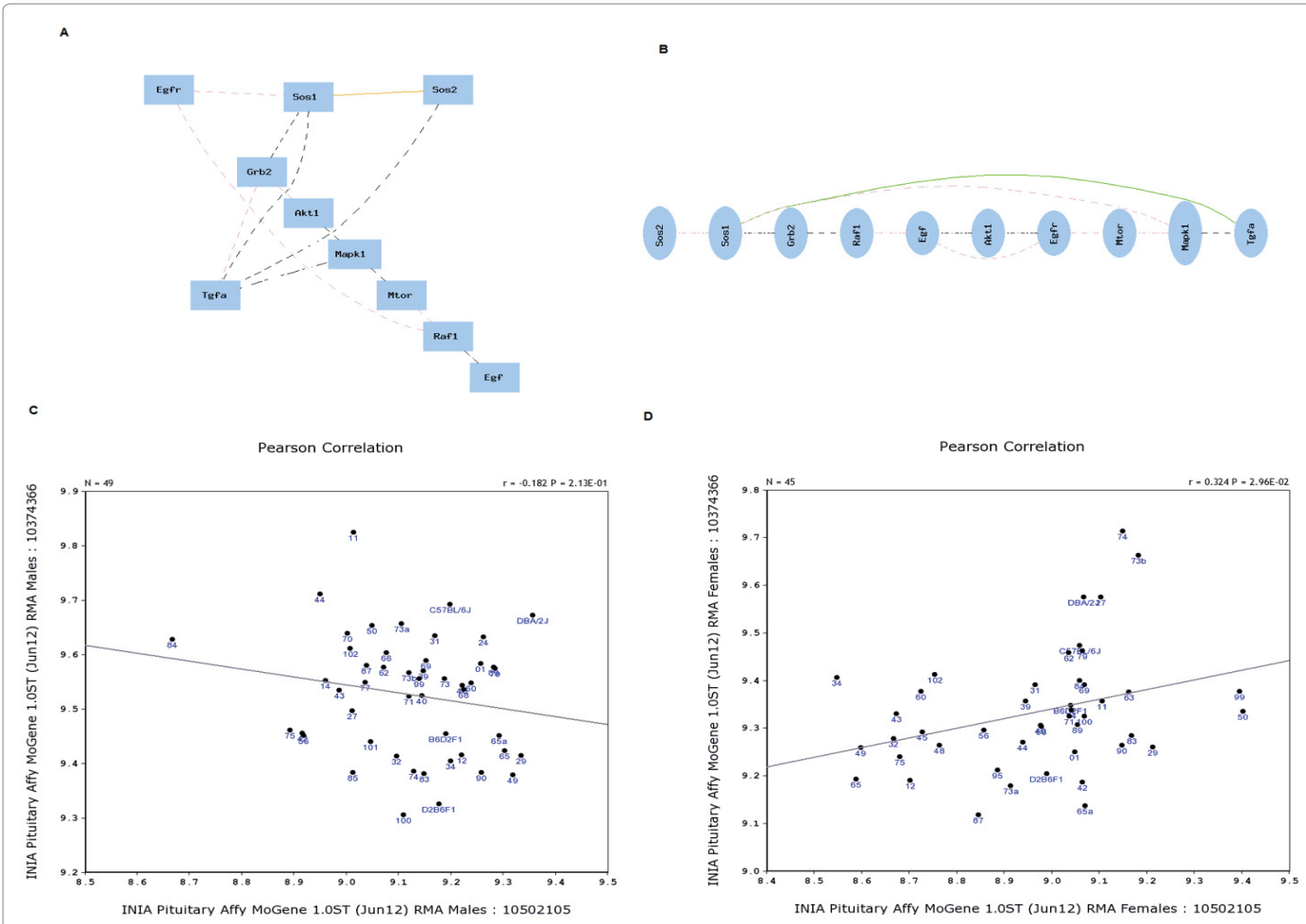

Figure 5: Gene network of known genes that are in the Egfr pathway in mouse pituitary gland. **5A:** Gene network of known genes that are in the Egfr pathway in male pituitary gland. The 10 nodes in the graph below show the selected traits. The 13 edges between the nodes, filtered from the 45 total edges and drawn as curves, show Pearson correlation coefficients greater than 0.25 or less than -0.25. The graph's canvas is 40.0 by 40.0 cm, and the node labels are drawn with a 14.0 point font, and the edge labels are drawn with a 10.0 point font. **5B:** Gene network of known genes that are in the Egfr pathway in female pituitary gland. The 12 edges between the nodes, filtered from the 45 total edges and drawn as curves, show Pearson correlation coefficients greater than 0.3 or less than -0.3. **5C:** No correlation in expression levels between Egf and Egfr in male mice. **5D:** shows positive correlation in expression levels between Egf and Egfr in female mice.

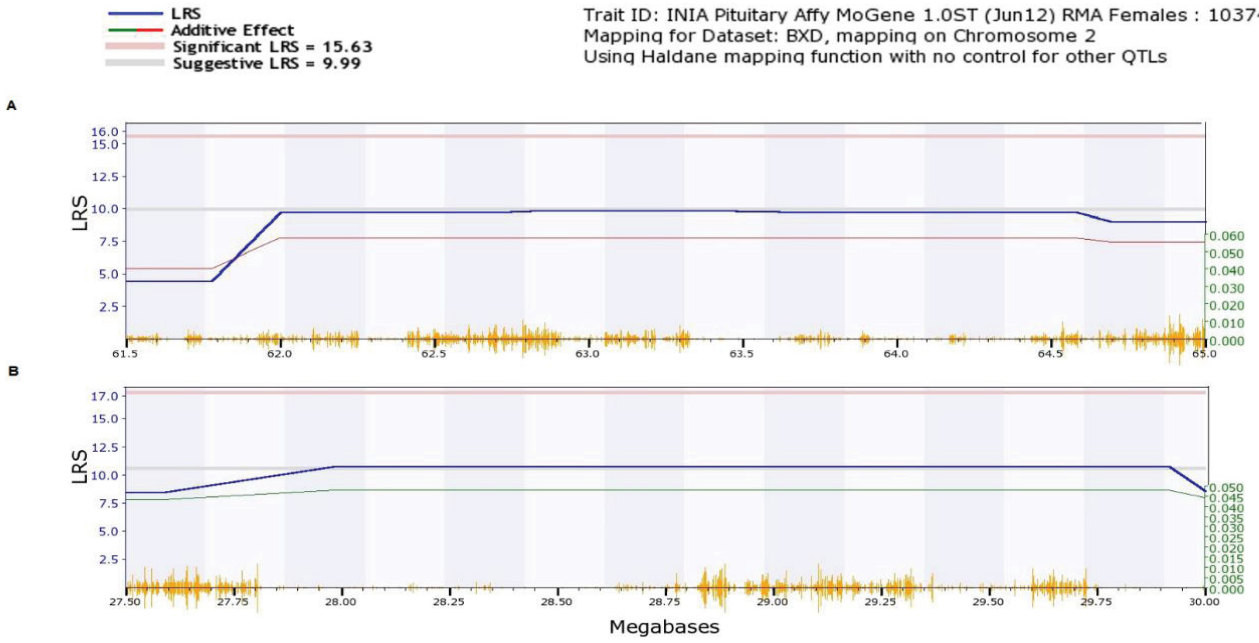

Figure 6: eQTL that regulate the expression level of Egfr in male and female mice. **6A:** The eQTL mapping results of QTL on chromosome 2 (Left) in female and chromosome 17 (Right) in male mice. **6B:** The genomic region of peak eQTL for the expression level of Egfr on chromosome 2 in female mice.

characterized an I-A-restricted T cell clone with dual specificity for poly(Glu60Ala30Tyr10) (GAT) and Mlsa, dl antigens including some which are isolated from mice of a small number of BXD strains [25]. Our data indicated that while the expression level of Egfr in male is not correlated to that of proliferation of T cell clone (JTL-G12 clone) without 50 ug/ml GAT, the expression level in female is strongly positively correlated to the proliferation of the T cell proliferation (Figures 7C and 7D). These data again suggest that while there is a gender difference on the effect of the expression levels of Egfr on the immunological function. Future study may help to explain a result of recently study that a significant association of EGFR copy number gain was found with tumor grade (P=0.044) and cirrhosis (P=0.015) exclusively in the male group in humans [26].

Discussion

This study is the first time to systematically investigate the sex differences of important immune pathways of Egfr using high quality data from pituitary gland from a mouse population of recombinant inbred (RI) strains. Pituitary gland secretes hormones that control variety of metabolic processes and organ functions. Because pituitary gland secretes hormones that control variety of metabolic processes and organ functions, it is essential to understand how these secretions are different between the female and the male. Egfr is an important drug target and it is secreted from pituitary gland. We identified several key genes that their expression levels are differentially associated to that of Egfr between female and male mice. Our study is the first step in understanding the differences in expression, gene network and regulation between the female and the male.

In the analysis of genes that their expression levels are most closely correlated to Egfr based on male mice, we found that several important genes are differentially associated to the Egfr between male and female mice. Very surprisingly, we found that Gas6 is highly associated with the expression level of Egfr in male but not in female. Gas6 is the major ligand of the receptor tyrosine kinase Axl In humans, AXL is a tyrosine kinase receptor activated by GAS6 and regulates cancer cell proliferation migration and angiogenesis. Increased expression of AXL and, in some cases, of its ligand GAS6 was found in EGFR-mutant lung cancers obtained from individuals with acquired resistance to tyrosine kinase inhibitors [27]. AXL has been used as the target for the drug development for cancers [28]. Thus the Egfr-Gas6-Axl axis has tremendous impact not only on the cancer growth but also on the resistance to drugs. The difference in the association between Egfr and Gas6 in male and female implicate the importance of gender consideration in drug design and therapeutic application. The other sex difference in the expression levels of Nrcam. The expression level of Nrcam is associated with Egfr in male but not in the female mice. Nrcam have been linked to several cancers [29,30]. High Nr-CAM expression is associated with favorable phenotype and late prostate-specific antigen (PSA) recurrence in prostate cancer treated by prostatectomy [29]. It's over expression is also associated with poor prognosis in advanced colorectal cancer [30,31]. Interestingly, its expression is also related to papillary thyroid carcinomas, glioblastoma and breast cancer [5,30,32]. Drugs targeting Egfr have been used for the treatment of variety of cancers. Our data suggest that gender difference in the response to the treatment should receive more attention. The third gene is the Klrb1a. In male, the expression level of Egfr is strongly negatively connected to the expression Klrb1a while in female mice there is no such a correlation. At present, Klrb1a has been linked to the inflammation [32]. Its role in cancer and drug resistance has not been explored. The importance of gender difference of the Egfr expression level is further demonstrated that its expression levels in male and female mice affect the T cell growth differently, implying the wide spectrum of the gender differential expression of Egfr on immune system.

Our analysis on the genes that are known important in the pathway of Egfr, we discovered that the association in the expression

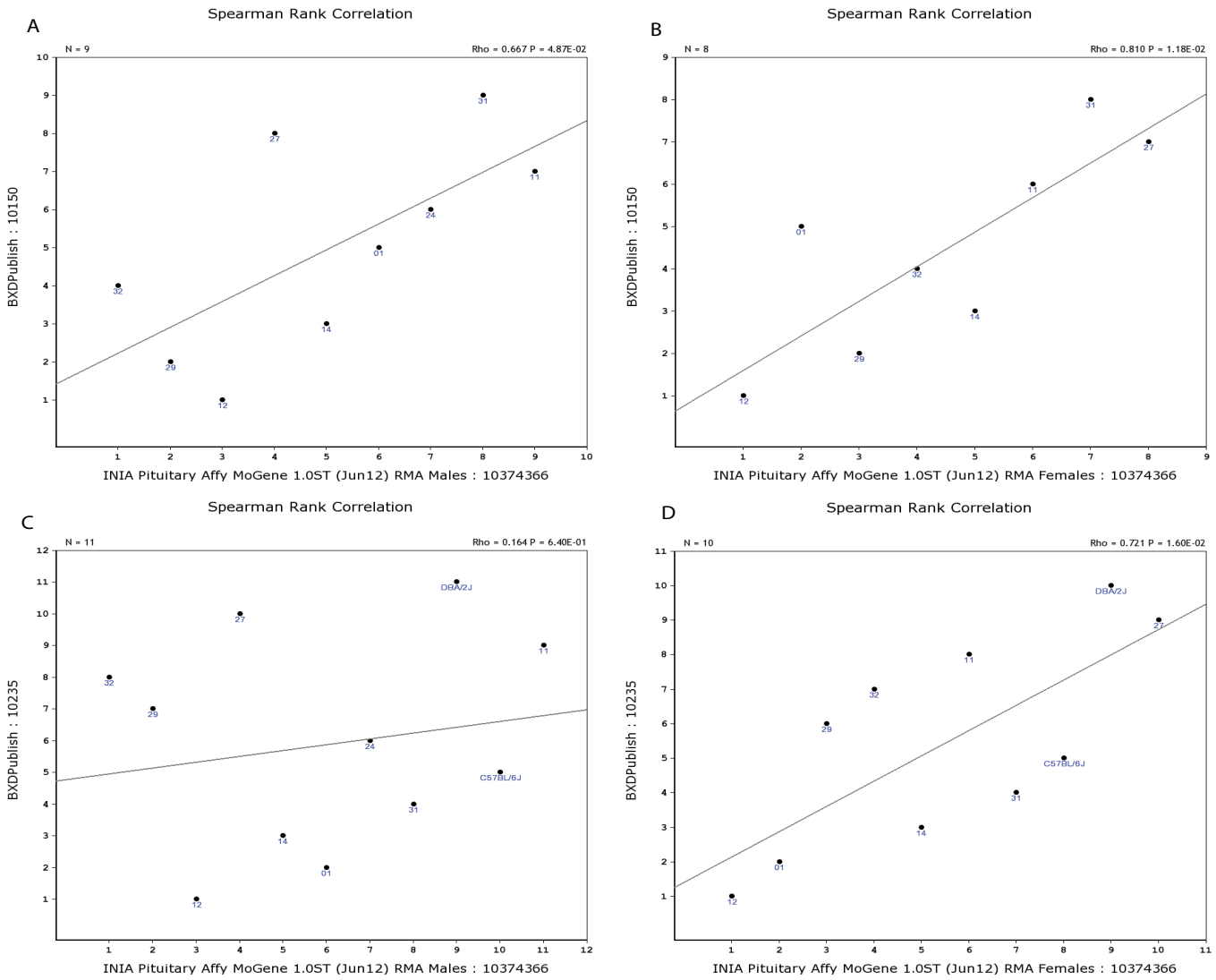

Figure 7: Correlation beteen Egfr expression levels in female and male pituitary gland and the growth of T cells. **7A:** Positive correlation between Egfr (probe 10374366) and T cell proliferative unresponsiveness (ID10150) in male. **7B:** Positive correlation between Egfr (probe 10374366) and T cell proliferetive unrespnsiveness (ID 10150) in female. **7C:** No correlation between Egfr (probe 10374366) and proliferation of T cell clone (ID 10235) in male. Positive correlation between Egfr (probe 10374366) and proliferation of T cell clone (ID 10235) in female.

level between Egfr and Egf are different between female and male mice. These findings agree with the fact that biologically there is a considerable difference in pituitary between men and women. This difference may influence the response to the drug treatment as Egfr is the target for the drugs of several cancers. We recognize that the variation in expression level represent the part of the function of a gene. Gene polymorphism and interact with other genes and genetic elements also alter the gene function [1,2]. Nevertheless, recognizing the sex difference in expression level is an important stepl for the drug design and therapeutic applications.

A clear limitation of this study is that the biological activity of pituitary changes throughout the life, while our analysis is at one time point. The difference in the association of genes from this study may or may not be different during other life stages. Or, it is very likely there are other difference in other life stages. However, recognizing such a difference brings the attention that future studies are necessary for this important issue.

In spite of the importance of the Egfr axis in immune diseases and cancers, and in spite of the sex differences of many immune diseases, the sex-specificity of Egfr has not yet been understood. Our study has initiated he first step toward understanding the sex-specificity of the Egfr axis.

Conclusion

There is significant difference in the Egfr pathways between female and male mice. Recognition of these differences may benefit drug target design, development, formulation and dosage determinant for pituitary tumors and immunological disorders in women and men in the clinical trials.

Acknowledgement

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