Genome-Wide Association Study For Local Histogram Emphysema Patterns Identifies Loci Near Chrna3/5 And Mmp12/mmp3

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Background: Quantitative measurements of emphysema extracted from CT scan data are a useful tool in COPD phenotyping, but existing quantitative phenotypes such as low attenuation area (LAA) % at -950HU have not found compelling genetic associations. Texture-based patterns of lung density in CT images may better characterize the amount and type of emphysema. Using a local histogram based emphysema classification method, we quantified the relative amounts of various types of emphysematous and normal lung tissue in CT scans from subjects in the COPDGene Study, and we performed a genome-wide association study on these quantitative phenotypes to identify genetic determinants of emphysema.
Methods: From the full COPDGene cohort of 10,276 individuals, 6,093 Caucasian subjects from the COPDGene Study with complete genotype and CT local histogram data were included in this analysis. Subjects received CT scans at full inspiration using a standard study protocol. For each CT scan, five local patterns of emphysema (normal lung, mild centrilobular emphysema, moderate centrilobular emphysema, severe centrilobular emphysema, and panlobular emphysema) were identified using a local histogram based method for emphysema detection in CT, and the percentage of lung tissue in each of these five categories was quantified. Each of these phenotypes (i.e. percent of lung corresponding to each of these five categories) was related to additively coded genotypes using a linear regression model simultaneously adjusting for age, gender, pack-years of cigarette exposure and principal components of genetic ancestry. Genotyping was performed using the Illumina Omni-Express array. After applying standard subject level and genotype level quality filters, 648,451 SNPs were available for association analysis.
Results: The correlation between the total amount of emphysema quantified by the local histogram method and LAA% at -950HU was 0.79. Correlations between the two emphysema quantification methods with FEV1 % of predicted were -0.61 and -0.63 for the local histogram method and for LAA% at -950HU, respectively. The correlations with pack-years were 0.27 (local histogram) and 0.20(LAA% at -950HU). Genetic association testing identified genome-wide significant associations for three related phenotypes (% of normal lung, moderate centrilobular emphysema, and severe centrilobular emphysema) at two loci near the CHRNA3/5 locus on 15q25 and near MMP12 and MMP3 on 11q22 (strongest associated SNPs rs1051730, p=1.2x10-12 and rs17368814, p=7.5x10-9).
Conclusions: Genetic markers near the CHRNA3/5 locus on 15q25 and near MMP12 and MMP3 on 11q22 are associated with local histogram measures of CT-quantitated emphysema at genome-wide significance.
QQ Plot for Severe Centilobular Emphysema GWAS

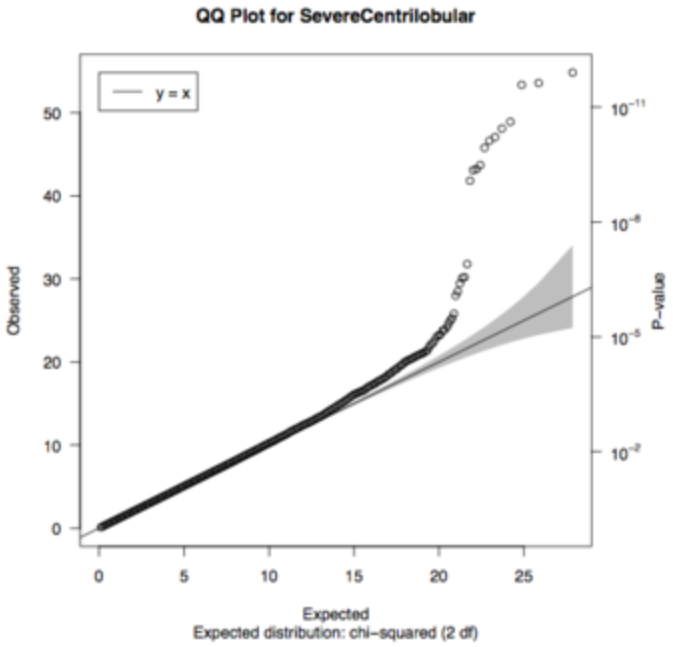

Figure 1. Genome-Wide Association QQ Plot for % Lung Classified as Severe Centrilobular Emphysema by CT Local Histogram Method in 6,093 Subjects from the COPDGene Study

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