The homeostatic iron regulator protein HFE is involved in regulation of iron acquisition for cells. The prevalence of two common HFE gene variants (H63D, C282Y) has been studied in many cancer types; however, the impact of HFE variants, sex and HFE gene expression in lung cancer has not been studied. We determined the prevalence of HFE variants and their impact on cancer phenotypes in lung cancer cell lines, in lung cancer patient specimens, and using The Cancer Genome Atlas (TCGA) database. We found that seven out of ten human lung cancer cell lines carry the H63D or C282Y HFE variant. Analysis of lung cancer specimens from our institute (Penn State Hershey Medical Center) revealed a sex and genotype interaction risk for metastasis in lung adenocarcinoma (LUAD) patients; H63D HFE is associated with less metastasis in males compared to wild type (WT) HFE; however, females with the H63D HFE variant tend to develop more metastatic tumors than WT female patients. In the TCGA LUAD dataset, the H63D HFE variant was associated with poorer survival in females compared to females with WT HFE. The frequency of C282Y HFE is higher in female lung squamous cell carcinoma (LUSC) patients of TCGA than males, however the C282Y HFE variant did not impact the survival of LUSC patients. In the TCGA LUSC dataset, C282Y HFE patients (especially females) had poorer survival than WT HFE patients. HFE expression level was not affected by HFE genotype status and did not impact patient's survival, regardless of sex. In summary, these data suggest that there is a sexually dimorphic effect of HFE polymorphisms in the survival and metastatic disease in lung cancer [1)].

In a study, Chiou et al. used a mouse model expressing a mutant form of the iron homeostatic regulator protein HFE, (Hfe H63D), the most common gene variant in Caucasians, to determine impact of the mutation on brain iron uptake. Iron uptake was assessed by using 59 Fe bound to either transferrin or H-ferritin as the iron carrier proteins. We demonstrate that at postnatal day 22, mutant mice brains take up greater amounts of iron compared to wildtype. Moreover, we introduce H-ferritin as a key protein in brain iron transport during development and identify a sex and genotype effect demonstrating female mutant mice take up more iron by transferrin while male mutant mice take up more iron from H-ferritin at PND22. Furthermore, we begin to elucidate the mechanism for uptake using immunohistochemistry to profile the regional distribution and temporal expression of transferrin receptor and Tim-2, the latter is the receptor for H-ferritin. These data demonstrate that sex and genotype have significant effects on iron uptake and that regional receptor expression may play a large role in the uptake patterns during development [2)].

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2)
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