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*HAGHL* genetic variants increase first fracture risk (FFR) in female childhood cancer survivors: A report from the Childhood Cancer Survivor Study (CCSS) and St. Jude Lifetime Cohort Study (SJLIFE)

**Background:** Recent genome-wide association studies (GWAS) have reported substantial sex differences in the genetic architectures of bone-related phenotypes. We investigated sex-specific genetic determinants of FFR in survivors of childhood cancer.

**Methods:** We performed sex-combined and sex-stratified GWAS for FFR using Cox regression models fitted on follow-up age in 2,453 long-term ( $\geq 5$  years) survivors in CCSS with  $\sim 5.4$  million imputed SNPs (minor allele frequency,  $MAF \geq 5\%$ ), with self-reported FFR defined by first fracture at any site after diagnosis. Replication analyses were conducted in an independent sample of 1,417 SJLIFE survivors with whole-genome sequencing and clinician-assessed FFR. All models were adjusted for relevant genetic (e.g., ancestry) and clinical (e.g., height, weight, treatment) factors.

**Results:** Sex-combined and male-specific analyses yielded no associations with  $P < 10^{-7}$ . Among female CCSS survivors ( $N=1,289$ ,  $33\% \geq 1$  fractures), we discovered 7 genome-wide significant ( $P < 5 \times 10^{-8}$ ) SNP-FFR associations with strong evidence of sex effect heterogeneity ( $P < 7 \times 10^{-6}$ ) across 2 independent loci with no known associations with bone phenotypes. We replicated these associations in SJLIFE ( $P \leq 0.05$ ) for 3 coding SNPs in the *HAGHL* gene (16p13.3), among which rs1406815 showed the strongest association ( $MAF=20\%$ , meta-analysis  $HR=1.43$ ,  $P=8.2 \times 10^{-9}$ ;  $N=1,935$  women,  $35\% \geq 1$  fractures). We observed increased *HAGHL* SNP effects on FFR that corresponded with increasing head/neck (HN) radiation therapy (RT) dose (Table). Public *omics* data show replicated SNPs are associated with differential *HAGHL* expression in sex gland and musculoskeletal tissues (GTEx) and in osteoblasts treated with dexamethasone or prostaglandins (GRASP), suggesting sex-/therapy-specific biological pathways involving *HAGHL* SNPs for fracture are plausible.

**Conclusions:** Novel associations between *HAGHL* genetic variants and FFR potentially reveal new sex- and therapy-specific biological mechanisms underlying bone-related health conditions in survivors of childhood cancer.

Table: rs1406815-FFR associations in female survivors stratified by HN RT dose.

HN RT strata	CCSS			SJLIFE		
	N strata	HR (95% CI)	P	N strata	HR (95% CI)	P
None	501	1.22 (0.95-1.57)	0.11	331	1.38 (1.03-1.85)	0.03
>0 Gy	788	1.88 (1.54-2.28)	$2.4 \times 10^{-10}$	315	1.14 (0.83-1.57)	0.43
>24 Gy	195	3.05 (1.95-4.76)	$9.1 \times 10^{-7}$	145	1.48 (0.85-2.57)	0.17
>36 Gy	117	3.79 (1.95-7.34)	$8.2 \times 10^{-5}$	61	3.08 (1.09-8.74)	0.03