A high-risk genetic profile for premature menopause (PM) in childhood cancer survivors (CCS) exposed to gonadotoxic therapy: A report from the St. Jude Lifetime Cohort (SJLIFE) and Childhood Cancer Survivor Study (CCSS).

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Abstract Text:

Background: CCS are at increased risk of therapy-related PM but contribution of genetic factors is unknown.
Methods: Using Affymetrix 6.0 SNP array, treatment exposures [cumulative alkylating agents (AA), ovarian radiotherapy (RT) dose] and clinically-assessed PM status (menopause < 40 years), a genome-wide association analysis was conducted using logistic regression in SJLIFE. A cluster of most statistically significant SNPs on chr4 was further examined, stratifying by ovarian RT and AA. Replication was performed using self-reported PM in CCSS.
Results: PM was diagnosed in 30 of 805 SJLIFE female survivors. A loci of 13 SNPs in 4 linkage disequilibrium blocks (mean $r^2 = 0.51$) in the upstream regulatory region of Neuropeptide Receptor 2 (*NPY2R*) was identified with a minimum p-value of 3.3×10^{-7} (all $< 10^{-5}$). ENCODE gene expression, motifs, and chromatin remodeling data suggest these SNPs alter transcription factor binding sites, potentially disrupting neuroendocrine events necessary for ovulation. Among CCS exposed to ovarian RT, homozygous carriers of a risk profile (RP) defined by 4 of the 13 SNPs, found in over half of the survivors with clinically-diagnosed PM and 1 in 7 in the general population, significantly increased PM risk (odds ratio (OR) 25.8, $p = 5.4 \times 10^{-5}$) (Table). This finding was replicated using self-reported PM status of 1644 survivors in CCSS (OR 4.2, $p = 4.6 \times 10^{-4}$). Prediction of clinically-diagnosed PM (in the SJLIFE discovery cohort) improved by adding the RP to the model with age and treatment (area under ROC curve 0.84 vs. 0.93, p = 0.011).
Conclusions: The common RP is associated with PM risk in pediatric cancer survivors and may have potential for clinical application. Table. SJLIFE discovery and CCSS replication

Treatment		**SJLIFE**			**CCSS**		
Ovarian RT	AA≥8 g/m^2	N (Clinically-diagnosed PM %)	RP OR (95% CI)	Exact P-value	N (Self-reported PM %)	RP OR (95% CI)	Wald P-value
No	No	490 (0.4)	5.9 (0.3-56.1)	0.099	1026 (2.0)	0.5 (0.1-2.3)	0.40

No	Yes	202 (2.5)	11.4 (1.8-72.5)	0.040	284 (9.2)	0.7 (0.1-2.4)	0.43
Yes	Yes&No	113 (20.4)	25.8 (6.2-137.4)	$5.4x10^{-5}$	334 (10.5)	4.2 (1.9-9.3)	$4.6x10^{-4}$