

# Genome-wide Association Study of Colorectal Adenoma Recurrence in the Selenium Trial



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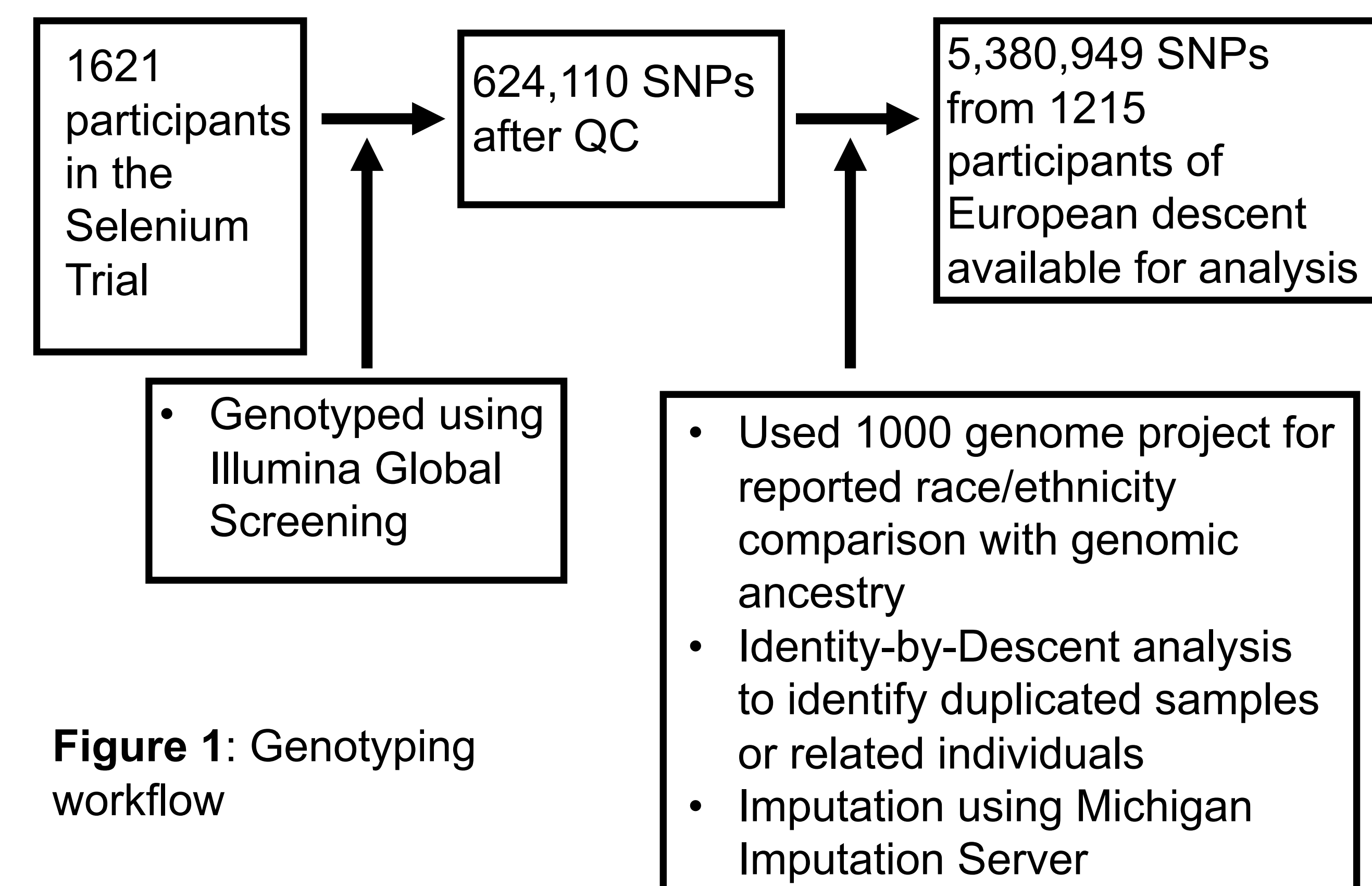
## BACKGROUND

- Genetic variation may be related to recurrent colorectal adenomas
- There have been no GWAS examining this relationship
- The Selenium Trial, a phase III, randomized, double-blind, placebo-controlled trial, examined the effect of selenium supplementation and adenoma recurrence
- Genetic variants associated with metachronous adenoma may help identify those at highest risk of adenoma development
- **Purpose:** Identify genetic variants that are associated with the development of metachronous colorectal adenoma



## METHODS

- Selenium Trial Inclusion Criteria:
  - Ages 40-80 years
  - Removal of at least one adenoma
  - No familial polyposis
  - No hereditary colorectal cancer
- There were 1621 participants in the selenium trial of which, 1215 were used for this analysis (**Figure 1**)
- Logistic regression analyses were used to identify genetic variants associated with overall adenoma recurrence, advanced metachronous adenoma and multiple metachronous adenoma
  - Adjusted for age, sex, randomization group and 3 principal components



**Figure 1:** Genotyping workflow

## RESULTS

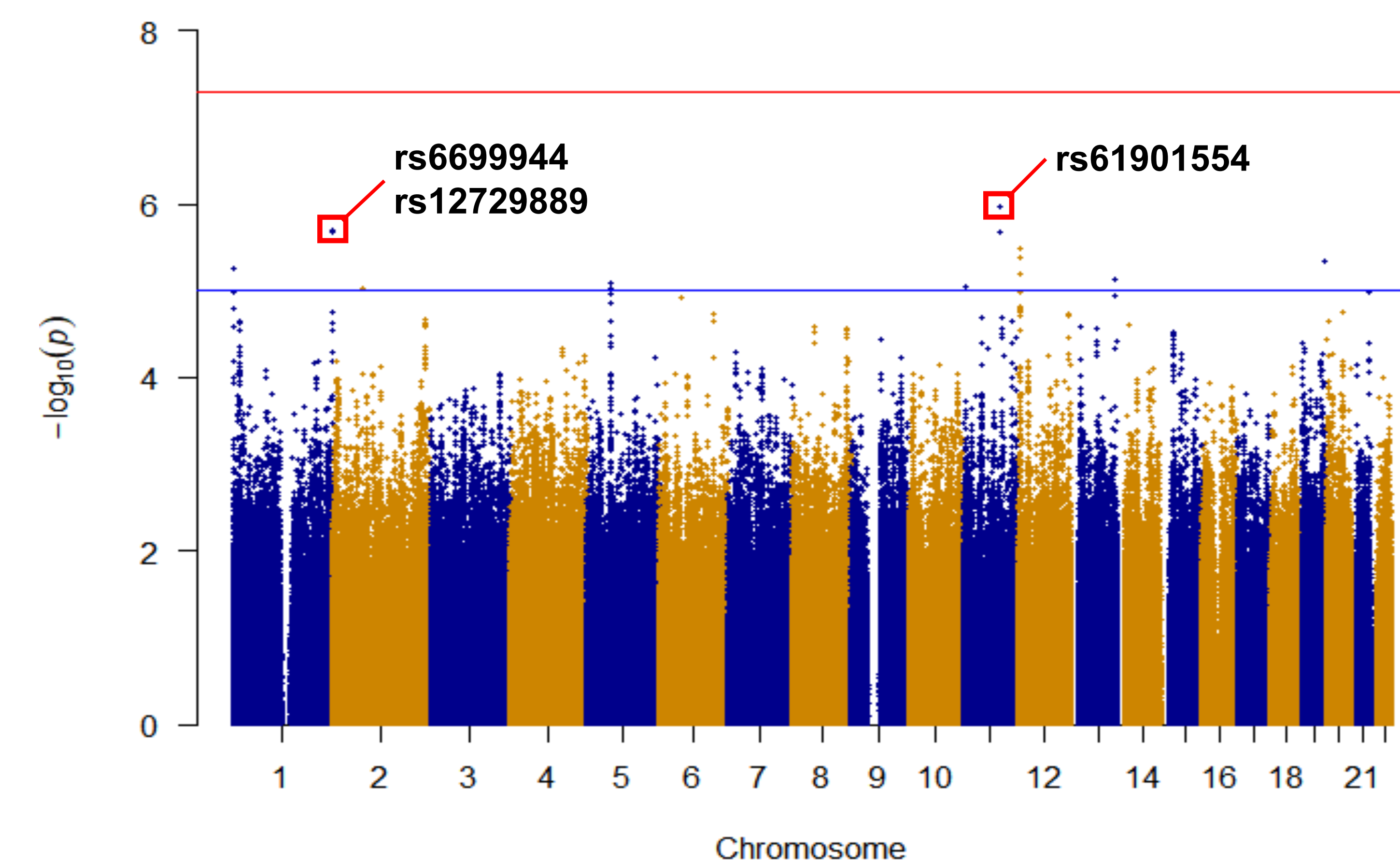
- On average, participants were 63 years old and mostly male (**Table 1**)
- Identified variants at two independent loci that are suggestively associated with adenoma recurrence ( $P < 10^{-5}$ ) [**Figure 2** and **Figure 3**]
  - rs61901554, an intron variant of FAT atypical cadherin 3 in the *FAT3* gene
  - rs12728998 and rs6699944 (in perfect linkage disequilibrium), in *NLRP3*, a gene encoding cryopyrin which forms inflammasomes

**Table 1:** Participant Characteristics

Characteristic	Total N=1215 (100%)	No Recurrent Adenoma N=681 (56%)	Recurrent Adenoma N=534 (44%)	P-Value
<b>Sex N(%)</b>				0.0002
Female	433 (35.6)	274 (40.2)	159 (29.8)	
Male	782 (64.4)	407 (59.8)	375 (70.2)	
<b>Age* Mean (SD)</b>	63.3 (8.8)	62.4 (9.1)	64.3 (8.4)	0.0001

\* at Randomization

**Figure 2:** Manhattan plot showing the association with adenoma recurrence

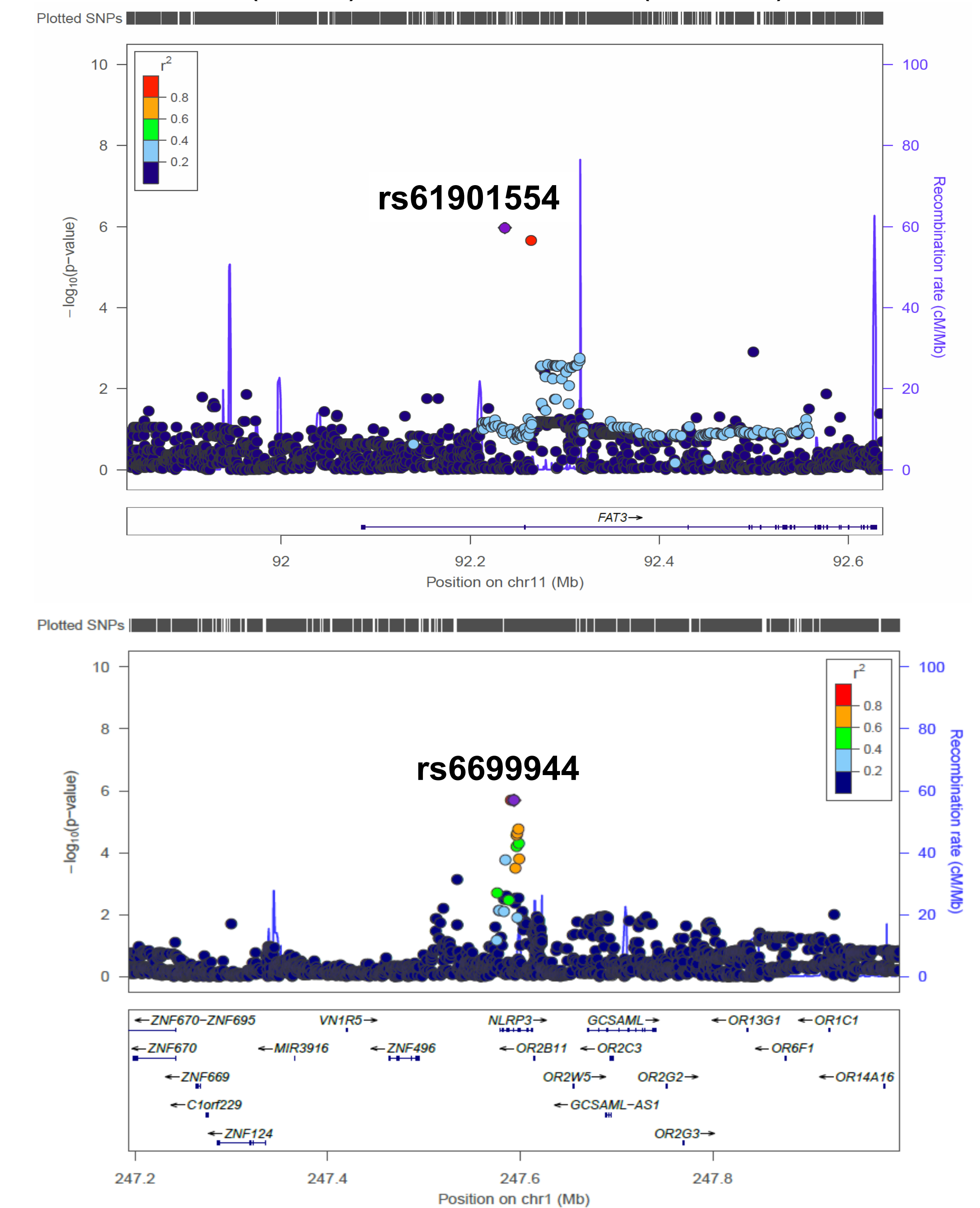


**Table 2:** Overall adenoma recurrence GWAS top SNPs.

SNP ID	CHR:BP	Gene	MA	Overall Adenoma Recurrence OR (95% CI) p-value	Multiple Metachronous Adenoma OR (95% CI) p-value	Advanced Metachronous Adenoma OR (95% CI) p-value
rs61901554	11:92236687	FAT3	T	1.67 (1.36, 2.06) $1.1 \times 10^{-6}$	1.46 (1.05, 2.04) 0.02	1.99 (1.42, 2.80) $7.9 \times 10^{-5}$
rs6699944 and rs12728998	1:247593562 1:247592175	NLRP3	A T	1.68 (1.36, 2.08) $2.0 \times 10^{-6}$	1.76 (1.27, 2.43) 0.0007	1.59 (1.12, 2.28) 0.01

\*CHR = Chromosome, BP = Base Pair, MA = Minor Allele

**Figure 3:** LocusZoom plots for overall adenoma recurrence top SNPs rs61901554 (*FAT3*) and rs6699944 (*NLRP3*).



## DISCUSSION

- First GWAS examining recurrent adenomas
  - Provides new insight into genetic basis of the development of metachronous adenoma
- *FAT3* has been previously found to be associated with advanced adenoma
- *NLRP3* has been previously found to be associated with poorer survival in colorectal cancer patients
- Limitations to our study include a small sample size, and no replication analysis at this point
- Variants may help identify those at highest risk of developing metachronous adenoma

## NEXT STEPS

- Replicate top hits in similar populations
- Explore region near *FAT3* gene

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