

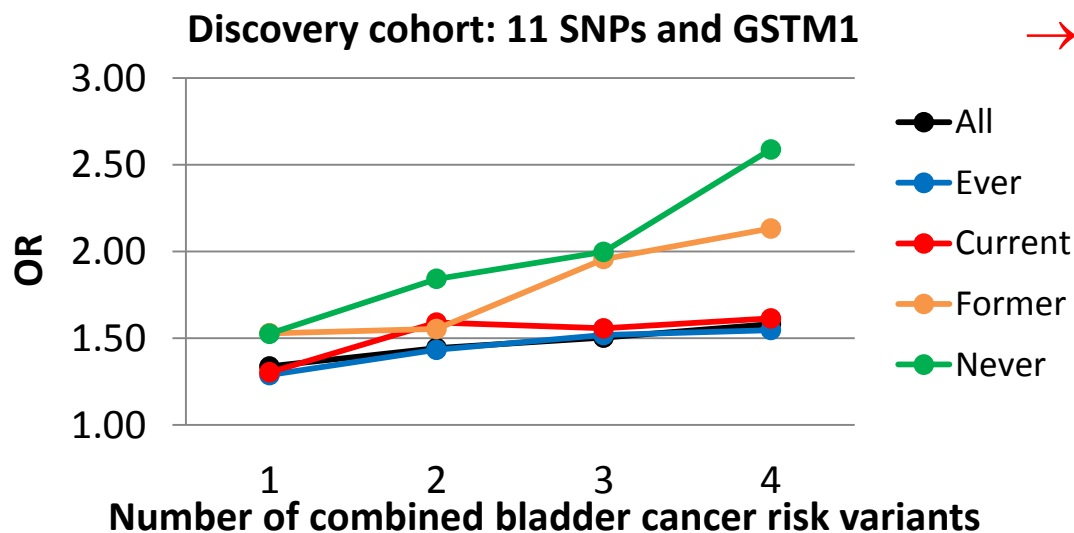
Identification and replication of the interplay of four genetic high-risk variants for urinary bladder cancer

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- 15 genomic regions identified by GWAS → higher UBC risk
- Combinations of SNPs still not investigated
- Analysis of 2-, 3- and 4-variant combinations: 12 genetic variants, totally 5049 cases and 5452 controls
- Discovery series: 2969 UBC cases/3285 controls (Germany, Netherlands), identification of best combinations (lowest P value)

Replication series: 2080 cases/2167 controls (The New England and Spanish Bladder Cancer Studies), replication



→ Highest OR in never smokers:

OR = 2.59, $P = 1.87 \times 10^{-10}$,
frequency: 25% in never smoking cases, 11% in never smoking controls

Replicated OR = 1.60, $P = 0.013$

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- Combinations of SNPs increase the individual risk significantly, especially in never smokers
 - Effects cannot be explained by the single SNP effects
 - Effects seem to depend on previous tobacco smoke exposure: 1.6-fold to >2.5-fold risks
 - Less exposure = more genetic risk
 - High exposure = less genetic risk
- Risk SNP combinations differ between smokers and never smokers

