Association between MICA polymorphisms, s-MICA levels, and pancreatic cancer risk in a population-based case-control study.

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Introduction

- The etiology of pancreatic cancer remains poorly understood. However, the immune system has been shown to play an important role in the development of pancreatic cancer.
- Abnormal cells express the transmembrane major histocompatibility complex class I chain-related gene A (MICA) protein, which is recognized by receptors present on NK (Natural Killer) and cytotoxic T cells.
- Pancreatic tumor cells release the MICA protein in soluble form (called s-MICA) from the tumor surface and thus avoid immune surveillance.
- In our previous study, a higher serum concentration of the s-MICA protein was associated with increased prevalence odds of pancreatic cancer.
- The MICA gene has a variable number of short tandem repeat (STR) polymorphisms consisting of four, five, six or nine GCT repeats, designated as A4, A5, A6, A7, A8, A9, A10, respectively. Additionally, the A5.1 allele contains an extra guanine (G) insertion resulting in a premature stop codon.

Goal of the study

- **Hypothesis**: Functional variants in the MICA gene are associated with circulating s-MICA levels and pancreatic cancer risk.
- We focused on the A5.1 MICA allele. This allele encodes a MICA protein that is shorter than its normal counterpart and is more easily cleaved from the cell surface.
- We hypothesized that having A5.1 MICA allele is associated with higher circulating s-MICA levels and increased pancreatic cancer risk.

Methods

- Pancreatic cancer cases were recruited in 1994-1998 from all hospitals in the seven-county metropolitan area of the Twin Cities and the Mayo Clinic, MN (N=116).
- Controls were recruited from
  - Drivers' license lists for individuals 20-64 years old
  - the US Health Care Financing Administration records for those aged 65+ years (N=492).
- The analysis was restricted to Caucasians (96% of all participants).
- Gene sequencing of exon 5 of the MICA gene was conducted by next-generation sequencing at the University of Minnesota Genomics Center.
- Allele assignments were based on the number of repeat units in the amplified regions of the MICA gene
- S-MICA levels were measured by enzyme-linked immunoabsorbent assay in the Cytokine reference laboratory.

Statistical analysis

•General linear regression with a log link was used to assess mean s-MICA levels across MICA alleles.

• Unconditional logistic regression was used to calculate the odds ratio (OR) and 95% confidence intervals (CI) for pancreatic cancer in relation to possessing at least once copy of MICA A5.1.

•Three statistical models were created and adjusted for:

- Model 1: Age, sex (modeled as continuous variables), education (no college vs some college), smoking status (never, former and current)
- Model 2: Model 1 plus alcohol consumption (no consumption, 1-6 servings per week and 7 or more servings per week), diabetes status (yes vs no)
- Model 3: Model 2, restricted to non-diabetic participants

Figure 1. Unadjusted s-MICA levels are higher among those with the MICA A5.1 polymorphism

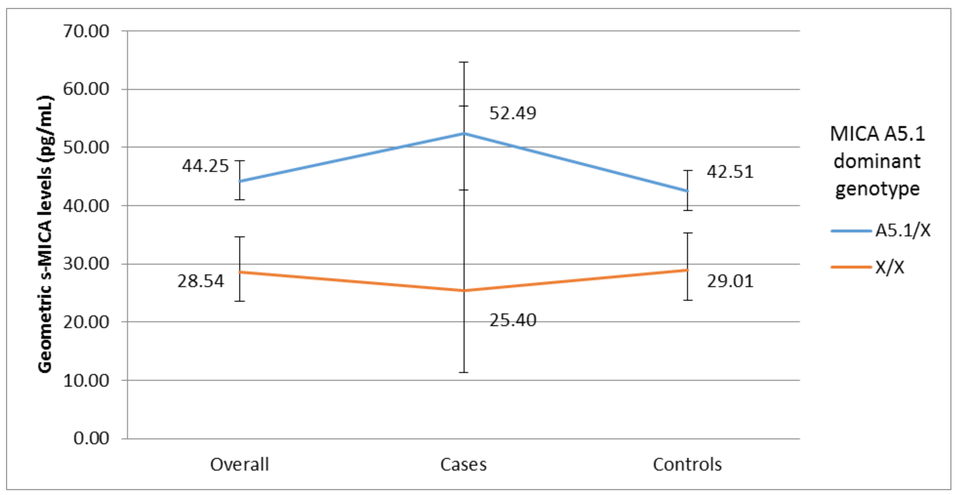


Figure 2. Adjusted s-MICA levels are higher among those with the MICA A5.1 polymorphism

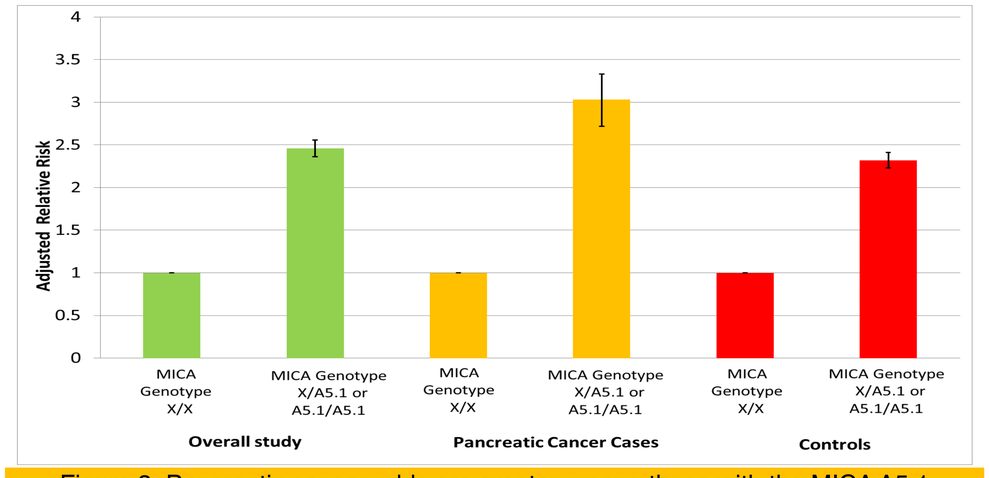
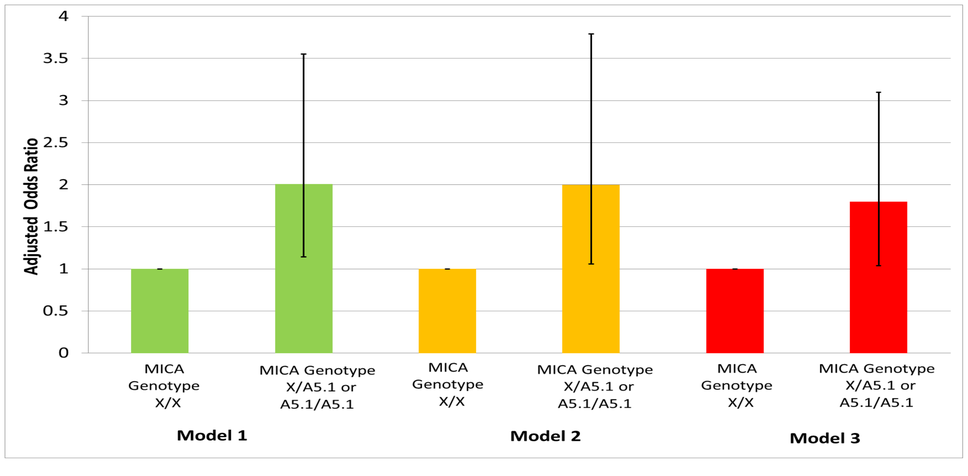


Figure 3. Pancreatic cancer odds are greater among those with the MICA A5.1 polymorphism



Results

- 452 participants (74%) possess at least one copy of the A5.1 allele, with 180 participants being homozygous and 272 participants being heterozygous for MICA A5.1
- After adjustment for confounders, participants with at least one copy of the MICA A5.1 allele had
  - 2.46 (95%CI: 2.36-2.56) times greater mean s-MICA levels than those without the A5.1 allele (Fig. 2).
  - greater pancreatic cancer risk (OR=2.00, 95% CI: 1.06-3.79) compared to those without any A5.1 allele (Fig. 3).
- There were no associations between other functional variants of the MICA STR polymorphism with pancreatic cancer risk or circulating s-MICA levels

Conclusions

- In this population-based case-control study, participants with at least one copy of the MICA A5.1 allele were at in increased risk of pancreatic cancer compared to those without any A5.1 allele.
- Participants with the MICA A5.1 allele had elevated circulating levels of s-MICA in both pancreatic cancer cases and controls.
- Our study supports the role of the MICA A5.1 allele in impaired immune response, which may increase the risk of pancreatic cancer.

Main citations

1. Xu X, Rao GS, Groh V, et al. Major histocompatibility complex class I-related chain A/B (MICA/B) expression in tumor tissue and serum of pancreatic cancer: role of uric acid accumulation in gemcitabine-induced MICA/B expression. *BMC Cancer*. 2011;11:194. doi:10.1186/1471-2407-11-194.
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3. Chen D, Gyllensten U. MICA polymorphism: biology and importance in cancer. *Carcinogenesis*. 2014;35(12):2633-2642. doi:10.1093/carcin/bgu215

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