Large Rearrangement Analysis in *GREM1* and the Identification of Novel Deletions and Duplications

Debora Mancini-DiNardo, Erin Mundt, Thaddeus Judkins, Jayson Holladay,
Karla R. Bowles, Benjamin B. Roa

Myriad Genetic Laboratories, Inc., Salt Lake City, UT

BACKGROUND

- Duplication of the *GREM1* regulatory region leading to changes in expression has been reported in patients with Hereditary Mixed Polyposis Syndrome (HMPS), a rare condition that has been identified in a small number of families to date.
- A 40kb duplication in the *GREM1* upstream regulatory region was reported as an Ashkenazi Jewish founder mutation in HMPS families.[1]
- Individuals with HMPS develop multiple colorectal polyps of varied types at young ages and have a significantly increased risk for colorectal cancer.

OBJECTIVE

- To report on our laboratory's experience with genetic testing for *GREM1* as part of a hereditary cancer panel.

METHODS

GENETIC TESTING

- Next generation sequencing (NGS) dosage analysis was designed to detect large rearrangements (LRs) in *GREM1* and the upstream region overlapping the adjacent gene *SCG5*.
- All LRs in *GREM1* were confirmed using MLPA.
- The known 40kb duplication[1] was further confirmed by breakpoint-specific PCR and sequencing analysis.

ANALYSIS

- LRs in *GREM1* detected between July 2016 and September 2017 were assessed.

RESULTS

- Seven unique LRs in *GREM1* (Figure 1) were detected in 35 individuals.
- Of the three published LRs involving *GREM1* (Figure 1),[1-3] only the Ashkenazi Jewish founder mutation (40kb duplication[1]) was reported here (Figure 2).
  - Two additional duplications were also detected and extend beyond the endpoints of the founder duplication (Figure 1).
  - NGS results for these duplications and the founder mutation are identical and LRs must be distinguished using MLPA and targeted PCR.
- The 40kb duplication was classified as likely pathogenic because of the collective supporting data.
  - There was insufficient data to definitively classify the other LRs involving *GREM1*, which were therefore classified as uncertain.

Figure 1. Schematic of NGS and MLPA coverage as well as nine observed LRs involving GREM1, two of which have been reported in the literature but not detected here.

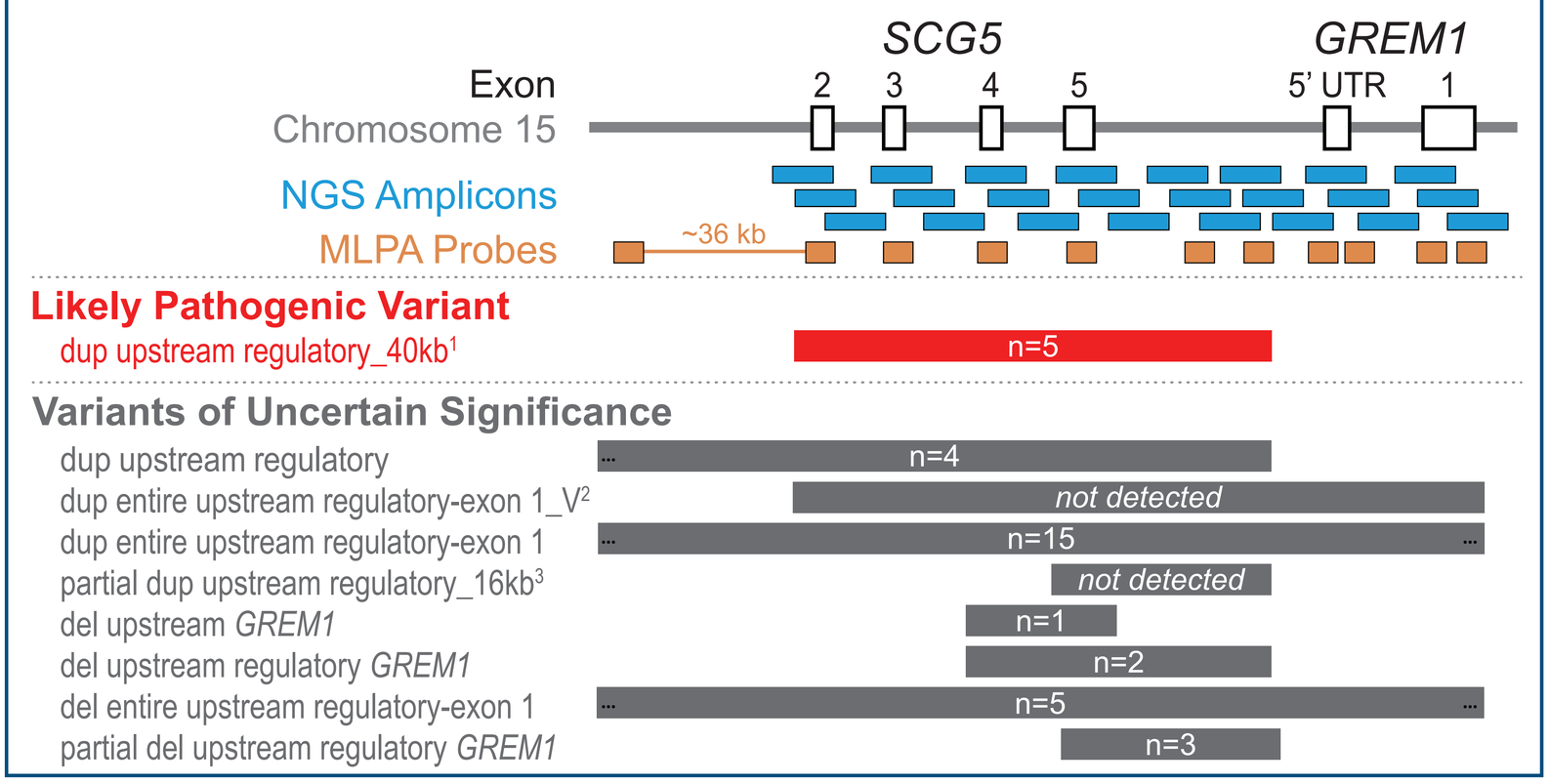
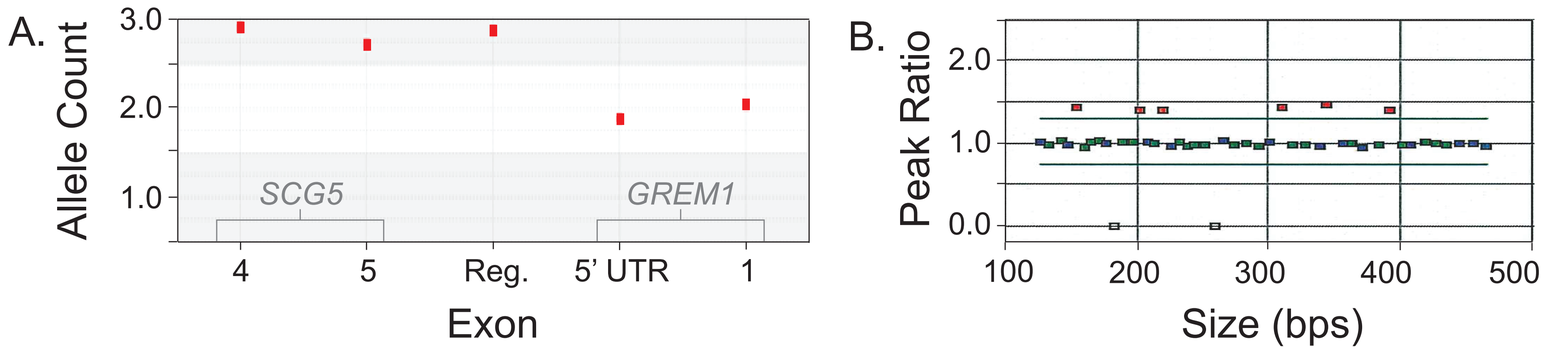


Figure 2. Representative NGS and MLPA data for the likely pathogenic 40kb duplication.

A) NGS showing a duplication of the region upstream of *GREM1* (red squares show average dosage; duplicated exons align to ~3) B) Confirmatory MLPA analysis (duplicated exons align to ~1.5).



CONCLUSIONS

- There are more variations in *GREM1* than previously reported, requiring further analysis and interpretation.
- Assessing regions upstream and downstream of *SCG5* exon 2 is critical to distinguish similar duplications, which may differ in clinical significance.
- Proper identification and interpretation of LRs detected in *GREM1* is essential to appropriate clinical management.

Presented at ASHG on October 18, 2017

REFERENCES

1. Jaeger et al. *Nat Genet*. 2012. 44:699–703.
2. Venkachatalam et al. *Int J Cancer*. 2011. 129:1635–1642.
3. Rohlin et al. *Int J Oncol*. 2014. 45:77–81.