Common variants in *PMS2CL* that can present in *PMS2* as pathogenic variants with extremely low frequencies

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BACKGROUND

- *PMS2*, a Lynch syndrome-associated DNA mismatch-repair gene,[1] often is included in next generation sequencing (NGS) hereditary pan-cancer panels.
- Molecular testing of *PMS2* is complicated by the interference of highly homologous pseudogenes.
  - The most homologous pseudogene, *PMS2CL*, is >98% identical to *PMS2* exons 11-15.[2]
- Therefore, additional analysis is required for variants identified in exons 11-15 to determine whether they are located in *PMS2* or *PMS2CL*.[3]
- Correct allocation of variants identified by NGS in this region is critical for proper clinical management.

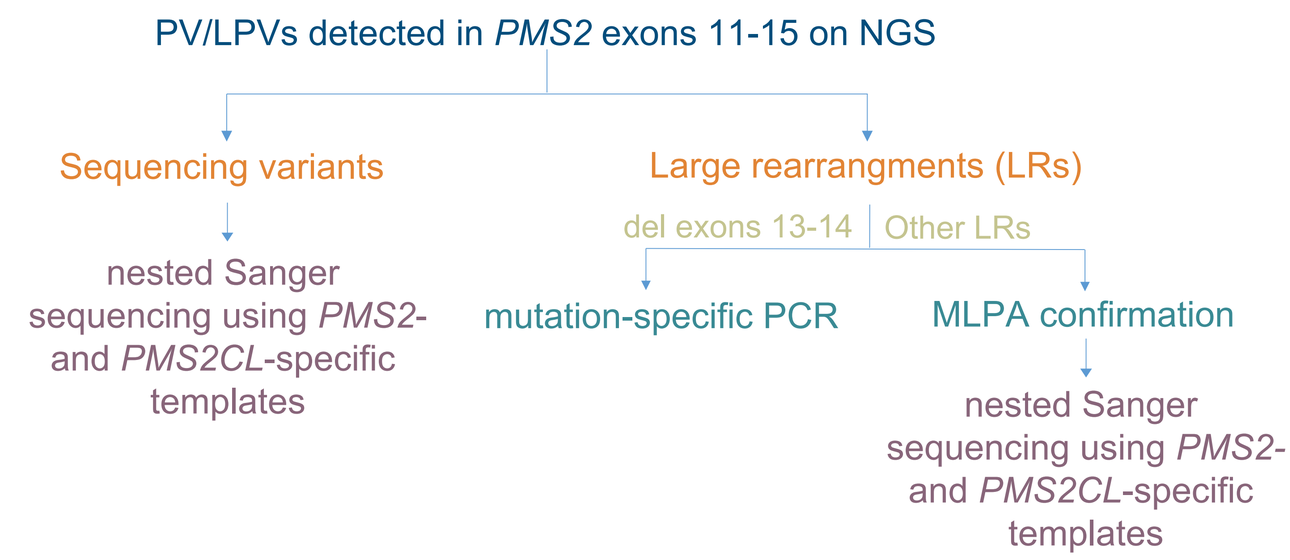
OBJECTIVE

- Evaluate the frequency of variants that predominantly occur in *PMS2CL* but can also be present in *PMS2* in extremely rare cases (<1%), with a focus on those that are considered pathogenic when they occur in *PMS2*.

METHODS

- Pathogenic/likely pathogenic sequence variants (PV/LPVs) detected from July 2016-April 2019 and large rearrangements (LRs) detected from May 2017-April 2019 in the region of *PMS2,* homologous to *PMS2CL* (exons 11-15), were evaluated in individuals tested on an NGS hereditary pan-cancer panel.
- These variants were initially identified by NGS, then their chromosomal location was confirmed in *PMS2* or *PMS2CL* with target-specific long range PCR (Figure 1).
- PV/LPVs were selected for this analysis if they had >100 observations upon NGS testing, but were confirmed to be in *PMS2* in <1% of cases.

Figure 1. Differentiating Variants in PMS2CL versus PMS2



RESULTS

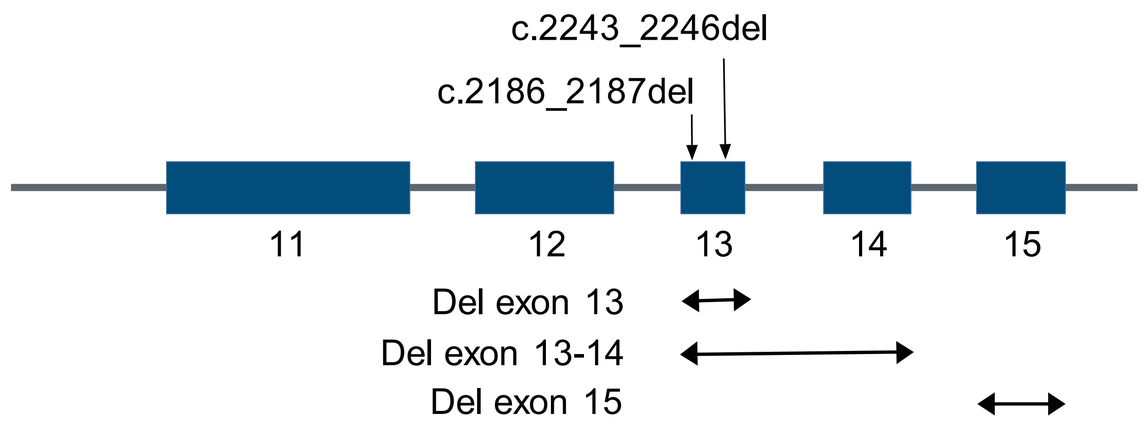
- Two sequence variants and three LRs were assessed (Table 1, Figure 2).
- Collectively, these variants were detected in 12,217 individuals (Table 1).
- In 99.91% (12,206/12,217) of cases, variants were confirmed orthogonally to be present in *PMS2CL* (Table 1).
- In 11 (0.09%) individuals, variants were located in *PMS2* (Table 1).
- The rarest PV in *PMS2* was c.2186_2187del (p.Leu729Glnfs*6).
  - Only one (<0.01%) patient was confirmed to carry this PV in *PMS2* (Table 1).

Table 1. Frequencies of Identified Variants in PMS2CL & PMS2

Variant	Total cases	*PMS2CL*		*PMS2*	
		# of cases	%	# of cases	%
c.2186_2187del*	7593	7592	99.99%	1	0.01%
c.2243_2246del **	2741	2739	99.93%	2	0.07%
del exons 13-14	992	990	99.80%	2	0.20%
del exon 13	620	616	99.35%	4	0.65%
del exon 15	271	269	99.26%	2	0.74%
Total	12217	12206	99.91%	11	0.09%

*p.Leu729Glnfs*6, **p.Lys748Metfs*19

Figure 2. Location of the Identified Variants



CONCLUSIONS

- Comprehensive testing in a large testing population enabled identification of PV/LPVs that are predominantly present in *PMS2CL* but can occur in *PMS2* in extremely rare cases.
- These data highlight the need to disambiguate PV/LPVs in *PMS2* versus *PMS2CL* and emphasize the importance of additional analysis for all potential PV/LPVs identified in the pseudogene region by NGS, even for those variants that occur in *PMS2CL* in >99.99% of the cases.
- We have demonstrated that, though rare, these variants can occur in *PMS2*.
- Failure to confirm the PV/LPV location can produce a false negative result with significant implications for clinical management.

References: 1. Lynch HT et al, *Eur J Cancer.* 1995; 2. De Vos M et al, *Am J Hum Genet.* 2004; 3. Vaughn et al, *Hum Mutat.* 2010

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