Supplementary figure 1. RaptorX predictions for MLH1 wild-type and mutant residue. (A) MLH1 wild-type. (B) MLH1 mutant residue c.1151T>A, p.V384D.
Supplementary figure 2. HE staining shows abnormal growth and shape of nucleus in tumor cells from the proband. (A) 100µm and (B) 50µm.
Supplementary Table 1. Case-control studies related to association of *MLH*:c.1151T>A variant with CRC susceptibility

| First Author | Year | Country (Ethnicity) | References |
|--------------|------|---------------------|------------|
| Wang Y       | 1998 | China (Asian)       | Wang, Y., et al. A novel missense mutation in the DNA mismatch repair gene hMLH1 present among East Asians but not among Europeans. Hum Hered, 1998. |
| Wang Y       | 2000 | China (Asian)       | Wang Y., et al. One of the etiological factors of digestive tract cancers in Chinese: the missense mutation Val384Asp in the hMLH1 gene. Zhonghu Yi Xue Yi Chuan Xue Zhi.2000. |
| Kim JC       | 2004 | Korea (Asian)       | Kim JC., et al. Genotyping possible polymorphic variants of human mismatch repair genes in healthy Korean individuals and sporadic colorectal cancer patients. Fam Cancer. 2004. |
| Zhang XM     | 2005 | China (Asian)       | Zhang XM., et al. Study on the relationship between genetic polymorphism Val384Asp in hMLH1 gene and the risk of four different carcinomas. [Article in Chinese]. Zhonghua Liu Xing Bing Xue Za Zhi. 2004. |
| Mei Q        | 2006 | China (Asian)       | Mei Q., et al. Single-nucleotide polymorphisms of mismatch repair genes in healthy Chinese individuals and sporadic colorectal cancer patients. Cancer Genet Cytogenet. 2006. |
| Ohsawa T     | 2009 | Japan (Asian)       | Ohsawa T., et al. Colorectal cancer susceptibility associated with the hMLH1 V384D variant. Mol Med Rep. 2009. |
| Wang D       | 2010 | China (Asian)       | Wang D., et al. Etiological role of Val384Asp in hMLH1 gene in familial colorectal cancer. Acta Univ Med Nanjing. 2010. |
| Peng HX      | 2016 | China (Asian)       | Peng HX., et al. Molecular analysis of MLH1 variants in Chinese sporadic colorectal cancer patients. Genet Mol Res. 2016. |
Supplementary Table 2. Meta-analysis studies relevant to association of *MLH:c.1151T>A* polymorphism with CRC susceptibility

| First Author | Year | Country | Reference |
|--------------|------|---------|-----------|
| Chen H       | 2015 | China   | Chen H, et al. Association between MutL homolog 1 polymorphisms and the risk of colorectal cancer: a meta-analysis. J Cancer Res Clin Oncol. 2015. |
| Zare M       | 2018 | Iran    | Zare M., et al. Relevance of hMLH1 -93G>A, 655A>G and 1151T>A polymorphisms with colorectal cancer susceptibility: a meta-analysis based on 38 case-control studies.REV ASSOC MED BRAS 2018 |
Supplementary Table 3. MLH1 heterozygous variant on chromosome 3 from exome data examined in multiple computational tools for LS-mCRC

| Family information       | Variant details                      |
|--------------------------|--------------------------------------|
| Chr. Position (hg19)     | Chr3: 37067240                       |
| Reference allele         | T                                    |
| Alternate allele         | A                                    |
| Gene                     | MLH1                                 |
| MIM                      | 120436                               |
| Gene Bank                | NM_000249.3                          |
| Exonic Function          | Missense SNV                         |
| cDNA position            | c.1151T>A                            |
| AA substitution          | p.V384D                              |
| Predicted domain         | MutL transducer domain               |
| Protein consequence      | Valine to Aspartate                  |
| Mutation taster          | 1, D                                 |
| Mutpred2                 | 0.786, Del                           |
| Polyphen2_HVAR           | 0.998,D                              |
| Polyphen2_HDIV           | 1.0, D                               |
| SIFT                     | 0.0, Dam                             |
| PROVEAN                  | -.5.22, Del                          |
| FATHMM score prediction  | -2.66,Dam                            |
| CADD score               | 33.0 Dam                             |
| Frequency in TGP         | 0.0051                               |
| Frequency in ExAC database | 0.0028                            |
| Frequency in EVS database | 7.7e-05                            |
| Variant status           | Reported (in eight studies)          |
| Allelic status           | Heterozygous                         |