

## **Germline deletions in the *EPCAM* gene as a cause of Lynch syndrome – preliminary studies in Polish population.**

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### **Abstract**

Lynch syndrome (clinically referred to as HNPCC – Hereditary Non-Polyposis Colorectal Cancer) is a frequent, autosomal, dominantly-inherited cancer predisposition syndrome caused by various germline alterations that affect DNA mismatch repair genes, mainly *MLH1* and *MSH2*. Patients inheriting this predisposition are susceptible to colorectal, endometrial and other extracolonic tumors. It has recently been shown that germline deletions of the last few exons of the *EPCAM* gene are involved in the etiology of Lynch syndrome. Such constitutional mutations lead to subsequent epigenetic silencing of a neighbouring gene, here, *MSH2*, causing Lynch syndrome. Thus, deletions of the last few exons of *EPCAM* constitute a distinct class of mutations associated with HNPCC. Worldwide, several investigators have reported families with *EPCAM* 3'end deletions. The risk of colorectal cancer in carriers of *EPCAM* deletions is comparable to situations when patients are *MSH2* mutation carriers, and is associated with high expression levels of *EPCAM* in colorectal cancer stem cells. A lower risk of endometrial cancer was also reported. The frequent occurrence of somatic deletions affecting the *EPCAM* gene as a second hit in tumors from *EPCAM* deletion carriers suggests that the localization of somatic events inactivating mismatch repair genes in Lynch syndrome is not random, but related to the underlying germline mutation. Our data from the studies of 55 patients with LS indicates that deletions of 8 and 9 exons of the *EPCAM* gene determine 7% of LS cases without MMR mutation.

In conclusion, *EPCAM* 3'end deletions are a recurrent cause of Lynch syndrome, and detection should be implemented in routine Lynch syndrome diagnostics.