Mismatch Repair Gene Deficiency and Genetic Anticipation in Lynch Syndrome: Myth or Reality?

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Lynch syndrome (LS) is characterized by the onset of hereditary colorectal cancer at an early age, along with a high frequency of synchronous and metachronous colonic and extracolonic tumors (gastrointestinal, endometrial, ovarian, and pancreatic tumors; transitional cell carcinoma of the ureter and renal pelvis; and many more).[1] A variant of LS is Muir-Torre syndrome (MTS), characterized by the presence of sebaceous skin adenomas and/or carcinomas and keratoacanthomas associated with visceral malignancies.[2] Both LS and MTS have been linked to germline mutations in mismatch repair genes *MLH1*, *MSH2*, *MSH6*, and *PMS2*. Recent updates on LS have also reported the possibility of a link with the presence of constitutional epimutations in *MLH1* and *MSH2* genes; in particular, the latter have been shown as secondary to deletions in the neighboring *EpCAM* gene and not associated with mismatch repair gene mutations.[3]

When considering the hereditary transmission of the LS phenotype, we have to call into question the recent debate on genetic anticipation. Such a phenomenon is commonly referred to as the progressively early age at onset of a hereditary disease in subsequent generations within a pedigree, usually associated with an increasing severity of the clinical phenotype.[4] It was described by Warthin in his case report on Family G (the family of the seamstress who emigrated from Germany to Michigan before the Civil War), in which he noticed "the cancer occurrence at an earlier age in subsequent generations."[5,6] Thereafter, few studies investigated the phenomenon of anticipation in LS, as well as the potential biomolecular mechanisms underlying it.

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Observation of LS cohorts supports intergenerational differences in disease onset consistent with anticipation; however, these must be viewed cautiously because of a variety of confounding factors and bias in the ascertainment of subjects. The cohort effect is often called into question as one of the main factors causing a bias in anticipation studies and has been incorporated into the development of genetic models and statistically excluded in data analysis. This has been evidenced particularly in breast cancer, but reports regarding other hereditary cancer settings are less documented, and the 2 phenomena are often difficult to differentiate.

The identification of the predominant phenomenon in many hereditary settings is highly debated. To date, despite many favorable clinical reports, a real anticipation in LS, such as the one described in others hereditary settings, is controversial.[7] For example a very recent report of a large family with LS followed up over 5 generations claims the absence of genetic anticipation in this syndrome.[8] Tsai and colleagues[9] suggested that the referred anticipation within the LS frame was probably the result of an ascertainment bias and cohort effects, but this hypothesis was discussed and criticized by Westphalen and colleagues.[10] The authors reported clear features of anticipation for *MLH1* mutation carriers[10] and revealed that, in their study population, genetic anticipation was more evident if the mutated allele was passed through the male rather than the female line. Nilbert and colleagues[11] studied a large Danish LS cohort, claiming the role of anticipation in the progressive decrease in age at onset, statistically excluding birth cohort effects bias.

However, it appears that anticipation in hereditary cancers is limited to 3 consecutive generations. The clinical limitation of anticipation to 3 consecutive generations was well documented by Stella and colleagues,[12] who reported a germline founder *MSH2* mutation clearly associated with an anticipation effect in 4 large families with LS and documented a decline in age at diagnosis in subsequent generations within the pedigree in the absence of a birth cohort effect.

Additional reports provided evidence that the *MSH2* founder mutation may be associated with anticipation. A parent-of-origin effect in a large family with LS with an *MHS2* founder mutation was reported by Green and colleagues.[13] Anticipation phenomenon was reported in

association with an exon 4 to 8 *MSH2* founder deletion; the authors observed, particularly in 1 family, that the difference in the age onset over 2 generations was 20 years.[14]

Our unpublished epidemiologic data concerning 4 large and apparently unrelated families sharing the same *MLH1* mutation in Southern Italy[15] show a clear anticipation phenomenon from 1 generation to the next both for colorectal cancer and endometrial cancer. The age of onset of approximately 35 cases of colorectal cancer and 18 of endometrial cancer was significantly lower, passing from the third to the fifth generation.

In other genetic syndromes, the expansion of trinucleotide repeats was well characterized as the mechanism responsible for anticipation,[16] but the molecular basis for the anticipation phenomenon in LS has not been yet described; some hypotheses are based on the progressive accumulation of germline mutations[12]and on the telomere attrition.[17] Telomere length attrition has been proposed as the mechanism responsible for anticipation in several diseases, such as congenital dyskeratosis and Li-Fraumeni syndrome. The hypothesis of a relationship between telomere length and genetic anticipation in LS is still under debate. Bozzao and colleagues[8] suggested that telomere dynamics differ between *MLH1* and *MSH2* mutation carriers, hypothesizing that gene-specific mechanisms can control cancer anticipation in patients with LS. Recently, Seguí and colleagues[18] claimed that telomere shortening cannot be the only explanation for anticipation.

In the end, there is no unanimous consensus about the anticipation phenomenon in LS,[19] and some doubts remain while evaluating the appropriateness of statistical methods for testing genetic anticipation in LS. However, National Comprehensive Cancer Network guidelines are the most commonly used for screening protocols in mismatch repair mutation carriers in clinical practice. Guideline recommendations suggest to start endoscopic surveillance at the age of 20 to 25 years, or 10 years before the earliest cancer diagnosis in the family. Surveillance protocols for extracolonic malignancies related to LS or MTS also follow specific guidelines,[20] but we think that patients should undergo tailored protocols based on the specific tumor spectrum expressed by family members and taking into account anticipation phenomenon as well. For example, the presence of sebaceous neoplasms in families with the MTS phenotype should lead not only to the standard clinical and instrumental surveillance for the increased risk of visceral neoplasms in LS but also to a specific dermatologic surveillance.[20] Additional epidemiologic studies on LS cohorts carrying founder mutations may help us clarify the effective existence of anticipation phenomenon and its impact on clinical and instrumental follow-up protocols for both LS and its variant MTS.

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