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Review

Colorectal adenomatous polyposis syndromes: Genetic determinism, clinical presentation and recommendations for care

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Colorectal polyposis
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Summary

Colorectal adenomatous polyposis constitutes a diverse group of disorders with different modes of inheritance. Molecular diagnosis of this condition has become more complex. In fact, somatic mosaicism for *APC* mutations now appears to be more frequent than previously thought and rare germline alterations of this gene may be implicated in patients tested negative for "classical" *APC* mutations (point mutations and large genomic rearrangements). Moreover, the knowledge concerning several aspects of the *MUTYH*-associated polyposis has improved since its first description in 2002 and germline mutations in new genes have recently been implicated in some cases of unexplained adenomatous polyposis. Genetic testing in probands and their relatives should be conducted in the context of pre- and post-test genetic counseling. The recent advent of New Generation Sequencing (NGS) techniques affords the opportunity to rapidly screen patients for a comprehensive panel of colorectal cancer susceptibility genes in a cost-effective fashion. This type of approach will probably replace the classical sequential approach based on clinical presumptive diagnoses in the near future. The risk of colorectal cancer is very high in affected patients in the absence of appropriate care. Clinical management is complex and should be provided in centers with special expertise in these diseases. This review focuses on the various colorectal adenomatous polyposis syndromes with special attention to more innovative and important aspects.

Mots clés
Polyposes adénomateuses colorectales
Cancer colorectal
Prédisposition génétique

Résumé

Les polyposes adénomateuses colorectales : déterminisme génétique, présentation clinique et prise en charge

Les polyposes adénomateuses colorectales correspondent à un groupe hétérogène d'affections à transmission autosomique dominante ou récessive. Les connaissances relatives à leur déterminisme génétique se sont enrichies au cours des dernières décennies et le diagnostic moléculaire est devenu plus complexe. Ainsi, il apparaît que certaines polyposes liées à APC *peuvent être dues à des altérations en mosaïque de ce gène ou à des mutations constitutionnelles d'un type rare, méconnues par les techniques d'analyse classiques. De même, de nouvelles données sont disponibles concernant la polypose associée à* MUYTH *et de nouvelles entités rares ont été*

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récemment décrites : polyposes liées à une mutation du gène de l'axine 2, des gènes POLE *ou* POLD1 *et à des mutations bi-alléliques des gènes* MMR. *L'étude génétique moléculaire est initiée chez un individu atteint (« cas index ») à l'occasion d'une consultation de génétique oncologique. Ses modalités sont en cours de transformation avec l'avènement récent et la mise à disposition des techniques de nouvelle génération, dites « à haut débit ». Un test moléculaire ciblé peut être proposé dans un second temps aux apparentés à risque du cas index après que la mutation causale a été identifiée. Le risque de cancer colorectal des individus atteints est très élevé en l'absence de prise en charge adéquate et complexe qui doit être mise en place au mieux au sein de centres experts. Cette revue a pour objectif de faire un « état des lieux » des connaissances relatives aux polyposes adénomateuses colorectales en se focalisant sur les aspects innovants.*

Introduction

Colorectal adenomatous polyposis constitutes a diverse group of disorders characterized by the development of multiple adenomatous polyps throughout the colon and a very high risk of colorectal cancer in the case of inadequate management. *APC*- *and MUTYH*- associated colorectal adenomatous polyposis are the two major entities, first described in 1991 and 2012, respectively. *APC*-associated polyposis is a highly penetrant autosomal dominant disease, whereas *MUTYH*-associated polyposis has an autosomal recessive mode of inheritance. Germline mutations of *AXIN2* are very rare, but this gene should be analyzed in colorectal adenomatous polyposis patients with ectodermal dysplasia and especially with severe tooth agenesis. Moreover, Polymerase Proofreading Associated Polyposis (PPAP) and Constitutional Mismatch Repair Deficiency (CMMRD) syndrome are two newly described rare syndromes that may be associated with multiple colorectal adenomatous polyps or attenuated polyposis (*table I*).

Identification of the causative mutation is an important objective that justifies genetic testing of at-risk relatives. Genetic testing should be conducted in the context of pre- and post-test genetic counseling. Clinical management is complex and

Table I
Colorectal adenomatous polyposis syndromes

Syndrome	Gene	Mode of inheritance	Cancer risk	Phenotypic manifestations
APC-associated colorectal adenomatous polyposis	*APC*	Autosomal dominant	Colorectal Duodenal Gastric Desmoid tumor Hepatoblastoma Thyroid Biliary system Pancreas Brain/central nervous system (medulloblastoma)	Dental abnormalities Osteomas Epidermoid cysts Lipomas Congenital hypertrophy of retinal pigment epithelium
MUTYH-associated colorectal adenomatous polyposis	*MUTYH*	Autosomal recessive	Colorectal Duodenal	Sebaceous adenomas and carcinomas Sebaceous hyperplasia
AXIN2-associated colorectal adenomatous polyposis	*AXIN2*	Autosomal dominant	Colorectal	Oligodontia Other ectodermal dysplasia manifestations
Polymerase Proofreading Associated Polyposis (PPAP)	*POLE* *POLD1*	Autosomal dominant	Colorectal Endometrial	
Constitutional Mismatch Repair Deficiency Syndrome (CMMRD)	*MSH6* *PMS2* *MLH1* *MSH2*	Autosomal recessive	Colorectal Other LS cancers[1] Hematological malignancies Brain/central nervous system tumors	Café au lait macules Areas of skin hypopigmentation Neurofibromas Pilomatricomas Hepatic adenomas Congenital malformations

[1]Lynch syndrome (LS) cancers: endometrial, gastric, ovarian, small intestine, biliary system, urothelial carcinoma (upper urinary tract).