MUTATIONS DES GÈNES POLE / POLD1

DNA-POLYMERASE PROOFREADING ASSOCIATED POLYPOSIS

COLLOQUE DES RESEAUX SAR et PRED-IdF
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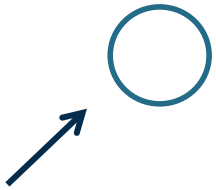
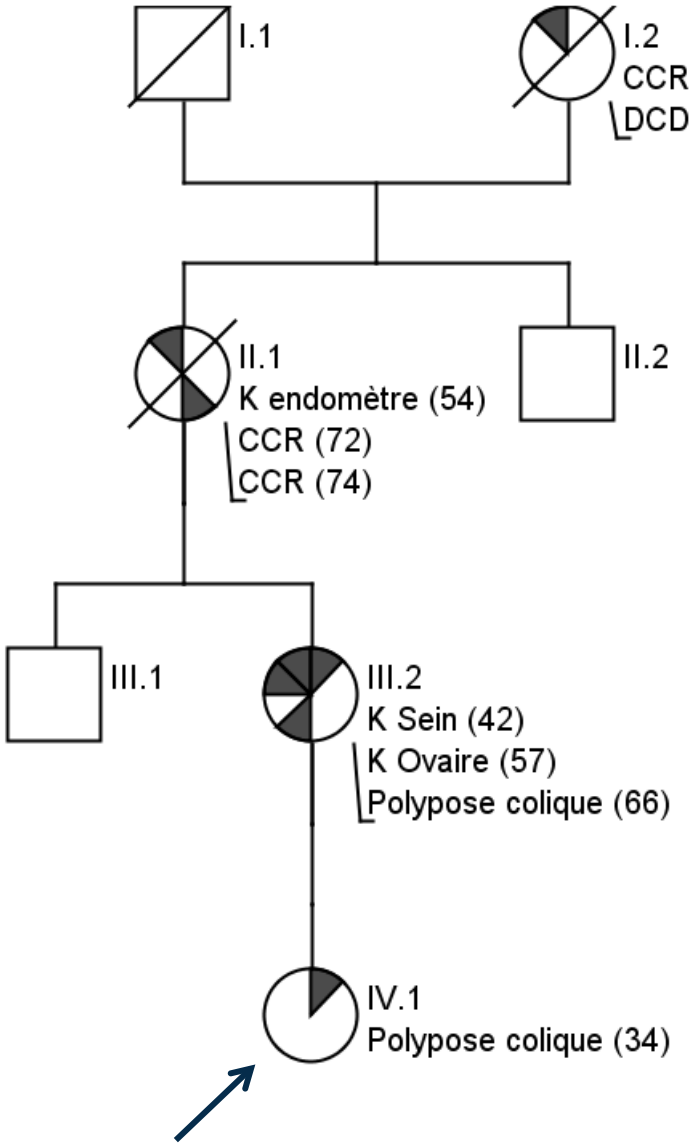
PRED-IdF

CAS CLINIQUE



2001 (34 ans)
Cs Oncogénétique devant ATCD personnels d'adénomes coliques (n=13)
ATCD familiaux de cancers coliques

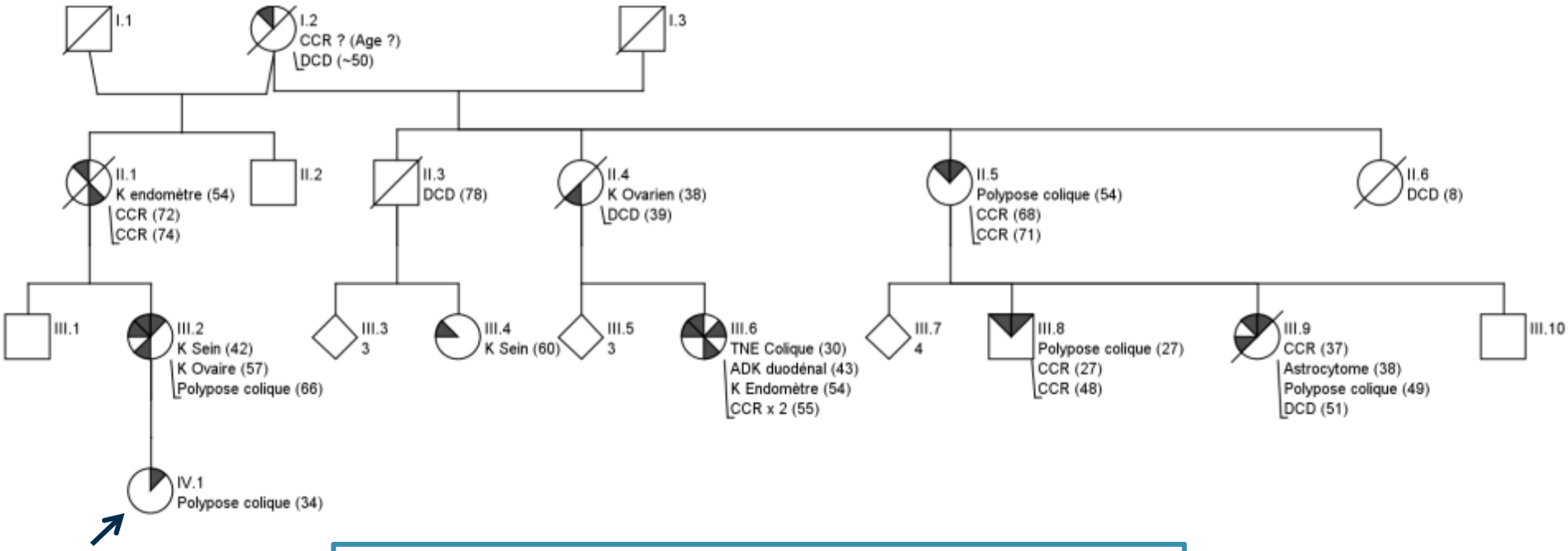


2001

- ✓ Pas évocateur *APC*
- ✓ *MutYH* non encore découvert
- ✓ Sd de Lynch? (mais beaucoup d'adénomes…)

IHC MMR et test RER sur adénomes :
PHENOTYPE MSS

2004



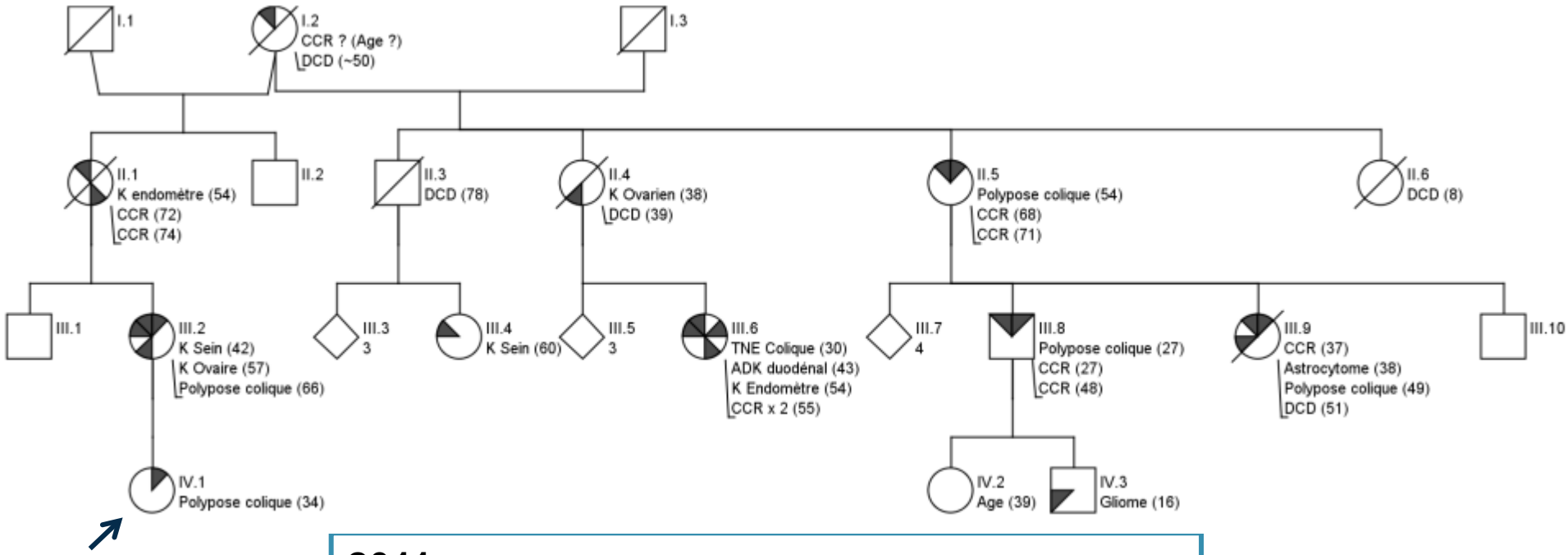
2004 :

Arbre complété après travail d'enquête familial

test RER sur CCR III.6 : MSS

Analyse gènes MMR, *APC* : VAIN

2011



2011 :

✓ **Cas Index :**

- Poursuite surveillance endoscopique / 2 ans
- Adénomes multiples à chaque examen

✓ **Mise à jour arbre:**

- Gliome

Analyse *MutYH* : VAIN

ARTICLES

nature genetics

Germline mutations affecting the proofreading domains of POLE and POLD1 predispose to colorectal adenomas and carcinomas

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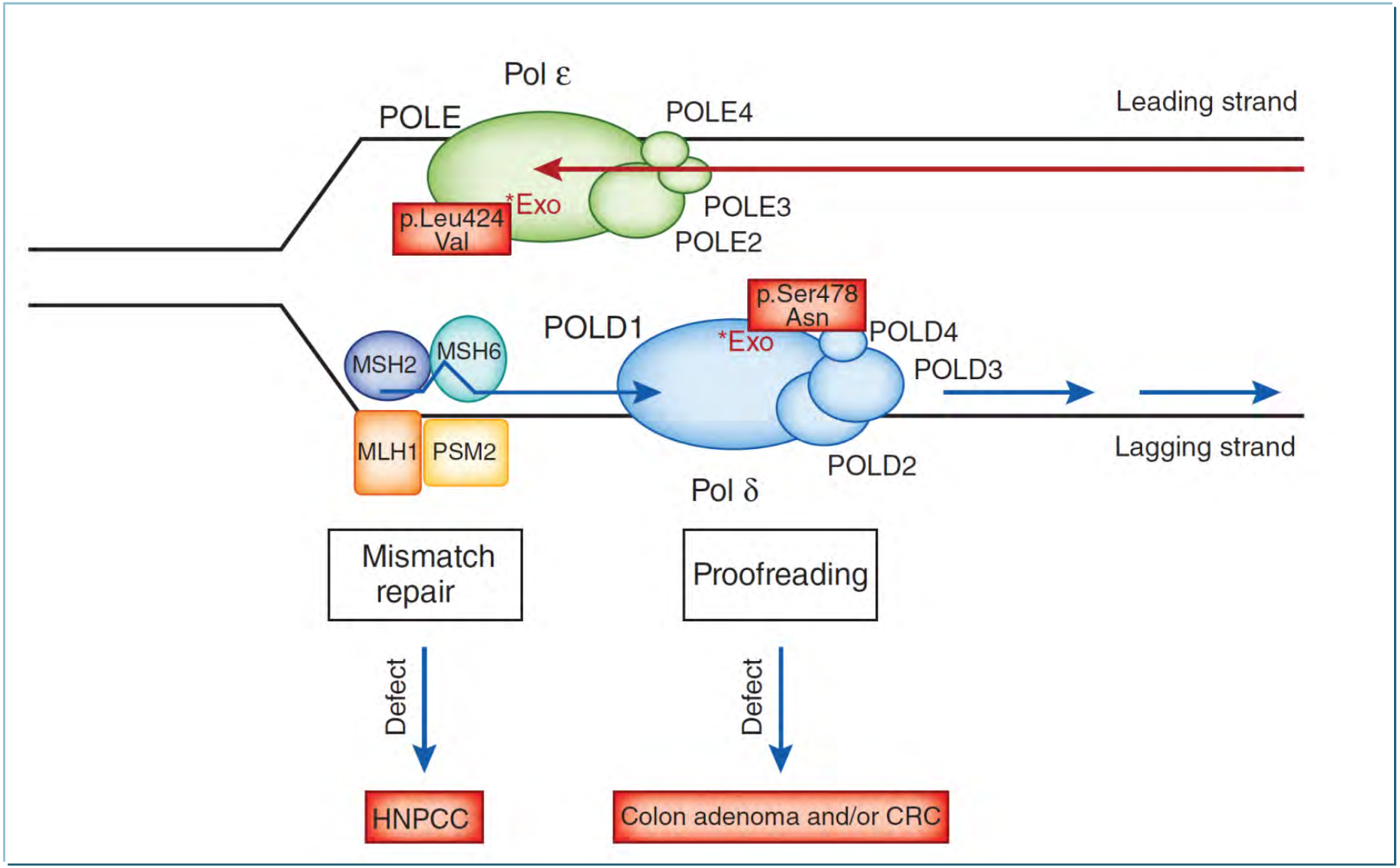
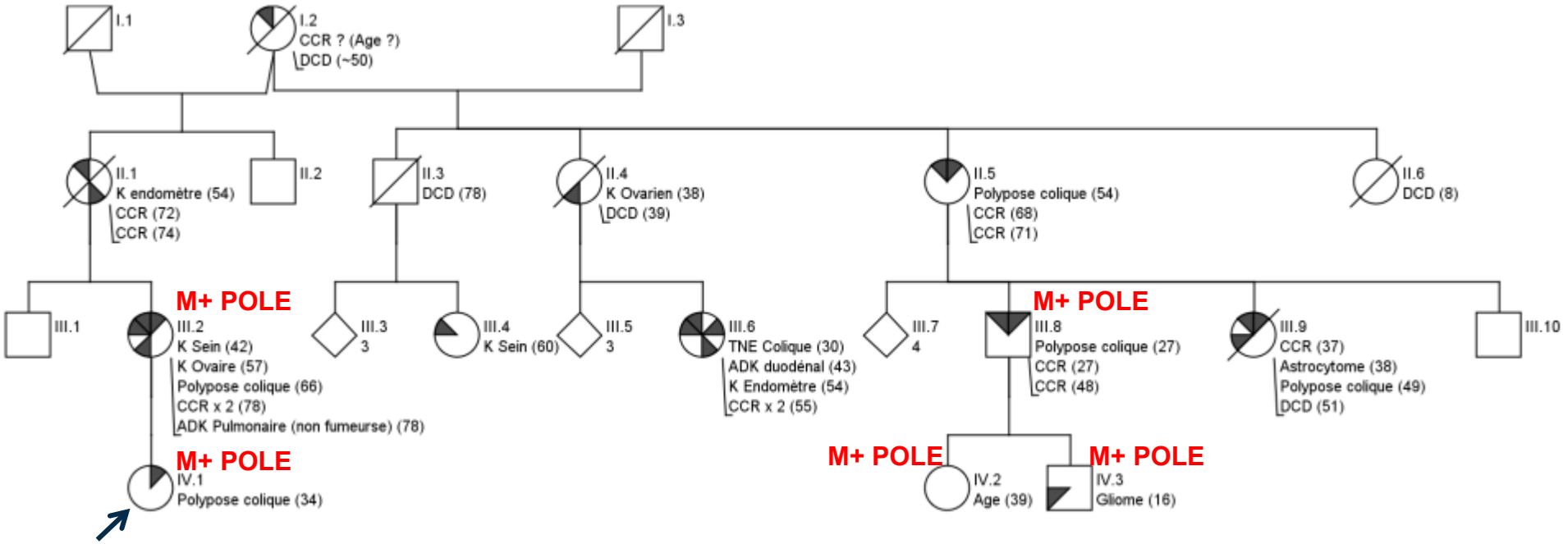


Fonction PROOFREADING
Fidélité de réplication de l'ADN

2017


I.1
I.2
CCR ? (Age ?)
DCD (~50)
I.3
II.1
K endomètre (54)
CCR (72)
CCR (74)
II.2
II.3
DCD (78)
II.4
K Ovarien (38)
DCD (39)
II.5
Polypose colique (54)
CCR (68)
CCR (71)
II.6
DCD (8)
III.1
M+ POLE
III.2
K Sein (42)
K Ovaire (57)
Polypose colique (66)
CCR x 2 (78)
ADK Pulmonaire (non fumeurse) (78)
III.3
3
III.4
K Sein (60)
III.5
3
III.6
TNE Colique (30)
ADK duodénal (43)
K Endomètre (54)
CCR x 2 (55)
III.7
4
M+ POLE
III.8
Polypose colique (27)
CCR (27)
CCR (48)
III.9
CCR (37)
Astrocytome (38)
Polypose colique (49)
DCD (51)
III.10
M+ POLE
IV.1
Polypose colique (34)
M+ POLE
IV.2
Age (39)
M+ POLE
IV.3
Gliome (16)

A panoply of errors: polymerase proofreading domain mutations in cancer

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Abstract | Although it has long been recognized that the exonucleolytic proofreading activity intrinsic to the replicative DNA polymerases Pol δ and Pol ε is essential for faithful replication of DNA, evidence that defective DNA polymerase proofreading contributes to human malignancy has been limited. However, recent studies have shown that germline mutations in the proofreading domains of Pol δ and Pol ε predispose to cancer, and that somatic Pol ε proofreading domain mutations occur in multiple sporadic tumours, where they underlie a phenotype of 'ultramutation' and favourable prognosis. In this Review, we summarize the current understanding of the mechanisms and consequences of polymerase proofreading domain mutations in human malignancies, and highlight the potential utility of these variants as novel cancer biomarkers and therapeutic targets.

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INVITED PERSPECTIVE

Germline and somatic polymerase ε and δ mutations define a new class of hypermutated colorectal and endometrial cancers

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Abstract

Polymerases ε and δ are the main enzymes that replicate eukaryotic DNA. Accurate replication occurs through Watson–Crick base pairing and also through the action of the polymerases' exonuclease (proofreading) domains. We have recently shown that germline exonuclease domain mutations (EDMs) of *POLE* and *POLD1* confer a high risk of multiple colorectal adenomas and carcinoma (CRC). *POLD1* mutations also predispose to endometrial cancer (EC). These mutations are associated with high penetrance and dominant inheritance, although the phenotype can be variable. We have named the condition polymerase proofreading-associated polyposis (PPAP). Somatic *POLE* EDMs have also been found in sporadic CRCs and ECs, although very few somatic *POLD1* EDMs have been detected. Both the germline and the somatic DNA polymerase EDMs cause an 'ultramutated', apparently microsatellite-stable, type of cancer, sometimes leading to over a million base substitutions per tumour. Here, we present the evidence for *POLE* and *POLD1* as important contributors to the pathogenesis of CRC and EC, and highlight some of the key questions in this emerging field.

Tumeurs HYPERMUTEES

RECOMMANDATIONS ACTUELLES DE SUIVI

- **AUCUNES OFFICIELLES…**

- **Au moins comme un Syndrome de Lynch**

  - ✓ Risque cérébral ???

  - ✓ Risque mammaire ???

PERSPECTIVES

- **RAPPORTER L'EXPERIENCE FRANCAISE**
  - ✓ Décrire nouvelles mutations
  - ✓ Améliorer connaissance phénotypiques
  - ✓ Rapporter résultats de tests fonctionnels
  - ✓ Faire proposition de suivi?