University of Groningen

Indication for CDKN2A-mutation analysis in familial pancreatic cancer families without melanomas

Harinck, Femme; Kluijt, Irma; van der Stoep, Nienke; Oldenburg, Rogier A.; Wagner, Anja; Aalfs, Cora M.; Sijmons, Rolf H.; Poley, Jan-Werner; Kuipers, Ernst J.; Fockens, Paul

Published in:
JOURNAL OF MEDICAL GENETICS

DOI:
[10.1136/jmedgenet-2011-100563](https://doi.org/10.1136/jmedgenet-2011-100563)

IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

Document Version
Publisher's PDF, also known as Version of record

Publication date:
2012

[Link to publication in University of Groningen/UMCG research database](#)

Citation for published version (APA):

Harinck, F., Kluijt, I., van der Stoep, N., Oldenburg, R. A., Wagner, A., Aalfs, C. M., Sijmons, R. H., Poley, J-W., Kuipers, E. J., Fockens, P., van Os, T. A. M., & Bruno, M. J. (2012). Indication for CDKN2A-mutation analysis in familial pancreatic cancer families without melanomas. *JOURNAL OF MEDICAL GENETICS*, 49(6), 362-365. <https://doi.org/10.1136/jmedgenet-2011-100563>

Copyright

Other than for strictly personal use, it is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), unless the work is under an open content license (like Creative Commons).

The publication may also be distributed here under the terms of Article 25fa of the Dutch Copyright Act, indicated by the "Taverne" license. More information can be found on the University of Groningen website: <https://www.rug.nl/library/open-access/self-archiving-pure/taverne-amendment>.

Take-down policy

If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

Downloaded from the University of Groningen/UMCG research database (Pure): <http://www.rug.nl/research/portal>. For technical reasons the number of authors shown on this cover page is limited to 10 maximum.

ORIGINAL ARTICLE

Indication for *CDKN2A*-mutation analysis in familial pancreatic cancer families without melanomas

Femme Harinck,¹ Irma Kluij, ² Nienke van der Stoep,³ Rogier A Oldenburg,⁴ Anja Wagner,⁴ Cora M Aalfs,⁵ Rolf H Sijmons,⁶ Jan-Werner Poley,¹ Ernst J Kuipers,^{1,7} Paul Fockens,⁸ Theo A M van Os,⁵ Marco J Bruno¹

► Additional figures are published online only. To view these files please visit the journal online (<http://jmg.bmj.com/content/49/6.toc>).

¹Department of Gastroenterology & Hepatology, Erasmus MC-University Medical Center Rotterdam, Rotterdam, The Netherlands

²Family Cancer Clinic, The Netherlands Cancer Institute, Amsterdam, The Netherlands

³Center for Human and Clinical Genetics, Leiden University Medical Center, Leiden, The Netherlands

⁴Department of Clinical Genetics, Erasmus MC-University Medical Center Rotterdam, Rotterdam, The Netherlands

⁵Department of Clinical Genetics, Academic Medical Center-University of Amsterdam, Amsterdam, The Netherlands

⁶Department of Clinical Genetics, University Medical Center Groningen-University of Groningen, Groningen, The Netherlands

⁷Department of Internal Medicine, Erasmus MC-University Medical Center Rotterdam, Rotterdam, The Netherlands

⁸Department of Gastroenterology & Hepatology, Academic Medical Center-University of Amsterdam, Amsterdam, The Netherlands

Correspondence to

Dr Femme Harinck, Erasmus MC-University Medical Center Rotterdam, Department of Gastroenterology & Hepatology, 's Gravendijkwal 230, 3015 CE Rotterdam, The Netherlands; f.harinck@erasmusmc.nl

Received 12 October 2011

Revised 11 March 2012

Accepted 16 March 2012

Published Online First

25 May 2012

ABSTRACT

Background *CDKN2A*-mutation carriers run a high risk of developing melanomas and have an increased risk of developing pancreatic cancer (PC). Familial PC (FPC) patients with a personal history or family history of melanomas are therefore offered *CDKN2A*-mutation analysis. In contrast, *CDKN2A* testing in FPC families without a history of melanomas is not generally recommended. The aim of this study was to evaluate the frequency of *CDKN2A*-mutations in FPC families without melanomas.

Methods Data were gathered from PC family registers. FPC families were defined as families with clustering of PC without meeting diagnostic criteria of familial cutaneous malignant melanoma (familial CMM) or other inherited cancer syndromes. Blood samples were obtained for DNA isolation from PC patients or first degree relatives and analysed for *CDKN2A*-mutations.

Results Among 40 FPC families, DNA analyses were carried out in 28 families (70%), leading to identification of *CDKN2A*-mutations in six families (21%). None of the *CDKN2A*-mutation-positive families fulfilled the diagnostic criteria for familial CMM and in three *CDKN2A* families no melanomas were observed. Two *CDKN2A*-mutations were found; the Dutch founder mutation p16-Leiden (c.225_243del, p.Ala76fs) and the c.19_23dup, p.Ser8fs-mutation. After disclosure of the *CDKN2A*-mutation in one of the families, a curable melanoma was diagnosed at dermatological surveillance in a 17-year-old family member.

Conclusion *CDKN2A*-mutation can be found in a considerable proportion of families with FPC. *CDKN2A*-mutation analysis should therefore be included in genetic testing in FPC families, even in the absence of reported melanomas. This strategy will enhance the recognition of individuals at risk for PC and facilitate the early detection of melanomas.

INTRODUCTION

Approximately 10% of all pancreatic cancer (PC) cases occur in a background of familial clustering.¹ In about 20% of these cases the underlying gene mutation is recognised.¹ One such inherited cancer syndrome with a known increased risk for PC is familial cutaneous malignant melanoma (familial CMM), referred to in the past as the familial atypical multiple mole melanoma syndrome (OMIM 155600).^{2–5}

This syndrome is characterised by the familial occurrence of melanomas⁵ and inherits as an autosomal dominant trait. Germ-line mutations in

CDKN2A have been found in at least a quarter of all melanoma prone families.^{6,7}

In addition to an increased risk of developing melanomas, *CDKN2A*-mutation carriers are also at risk of other types of cancer, particularly PC.^{2–4} Previous studies have shown that the risk of developing PC among *CDKN2A* carriers may be 50 times greater than in the general population.³

Therefore, families with any combination of PC and melanomas should be offered *CDKN2A* analysis.^{8–14} However, *CDKN2A* analysis is not recommended in families with a clustering of PC but without melanomas.¹⁰

The aim of this study was to evaluate the frequency of *CDKN2A*-mutations in familial PC (FPC) families without melanomas.

MATERIALS AND METHODS

Patients and families

We conducted a retrospective cohort study. Data were gathered from PC family registries from four Dutch clinical genetic centres (Academic Medical Center Amsterdam, Erasmus MC-University Medical Center Rotterdam, University Medical Center Groningen and the Netherlands Cancer Institute-Antoni van Leeuwenhoek Hospital). The total number of PC families was 70. Based on their phenotype, PC families were divided into FPC families (n=40) and syndromic PC families (n=30).

FPC families were defined as families with clustering of PC (≥ 2 first degree relatives (FDR), ≥ 3 relatives (FDR or second degree relatives (SDR)) or two SDR relatives, one <50 years at diagnosis) and not meeting diagnostic criteria of known inherited cancer syndromes (listed below).¹⁰ Syndromic PC families were defined as families with a known inherited cancer syndrome predisposing them to PC (including familial CMM, Peutz-Jeghers, Lynch, Li-Fraumeni and hereditary breast and ovarian cancer syndromes). The diagnosis of familial CMM was made based on the Dutch clinical criteria of familial atypical multiple mole melanomas in either ≥ 2 affected FDR or ≥ 3 affected relatives (FDR and/or SDR).¹⁵ The total number of familial CMM families within the cohort of syndromic PC families was 16 (53%).

In this study, we included only the FPC families and analysed whether DNA-mutation analysis for *CDKN2A/CDK4* was performed, and if so what the outcome of this mutation analysis was. DNA, either from blood samples or available paraffin embedded tumour samples, originated from individuals affected with PC or, in families without

available DNA from affected individuals, from healthy FDRs. For each family, a complete three-generation pedigree was made. Clinical diagnoses reported by patients and family members were verified by a review of medical and pathological records, and by revision of histological slides whenever available. At the time of genetic counselling, patients or their family members had given written informed consent to use the DNA results for future research projects.

All individuals from *CDKN2A*-mutation-positive families were advised to undergo dermatological examination to detect dysplastic nevi and/or melanoma.

***CDKN2A/CDK4*-mutation analysis**

Direct sequencing of all *CDKN2A* exons and *CDK4* exon 2 was performed on samples from the index cases, and subsequently on relatives of mutation-positive cases. In brief, all exons with flanking intronic regions were amplified by PCR using the following primers: *CDKN2A*-EX1BF 5'-GTGCGTGGGTCCCA GTCT-3', *CDKN2A*-EX1BR 5'-TAGCCTGGGCTAGAGACG AA-3' (Ta=57°C), *CDKN2A*-EX1AF 5'-TTCGCTAAGTGCTC GGAGTT-3', *CDKN2A*-EX1AR 5'-GAGAATCGAAGCGCTA CCT-3' (Ta=57°C), *CDKN2A*-EX2F 5'-GGAAATTGGAAGTGAAGC-3', *CDKN2A*-EX2R 5'-GCTGAACCTTCTGTGCTGGA AAAATG-3' (Ta=55°C), *CDKN2A*-EX3F 5'-GCAGTGGACTA GCTGCTGGA-3', *CDKN2A*-EX3R 5'-TTTACGGTAGTGGGG GAAGG-3' (Ta=57°C) and *CDK4*-EX2F 5'-TTGTTGCTGCAG GCTCATAC-3', *CDK4*-EX2R 5'-TCAGGTCCTCCACTTCTC TA 3' (Ta=57°C). All primers were flanked with respectively m13forward or reverse tags to allow direct sequencing. PCR reactions were carried out using GoTaq® DNA Polymerase (Promega, Benelux b.v.) based on the standard protocol at annealing temperature (Ta) as indicated at the primers. Subsequently, the sequence PCR products were analysed on an ABI3730 sequencer using BigDye® Terminator v3.1 Cycle Sequencing Kit (Applied Biosystems, Foster City, California, USA) and genotypes were assigned using SeqScape software (Applied Biosystems). The reference sequences for *CDKN2A* and for *CDK4* respectively with GenBank accession numbers NT_008413 v17 and NC_000012 v10 were used to analyse the sequence results and all detected variants were described according to the HGVS nomenclature recommendations.

CNV analysis of *CDKN2A* was performed for all samples by Multiplex Ligation-dependent Probe Amplification using the MRC-Holland probe-mix ME024-A1 (MRC-Holland, Amsterdam, Netherlands) as indicated by the manufacturer. CNV data for the *CDKN2A* region specific probes were analysed using GeneMarker software package (SoftGenetics, Pennsylvania, USA).

Data analyses

Continuous variables are presented as mean (SD) or median (IQR), where appropriate. Continuous variables were compared using the t test or the Mann-Whitney test. Categorical variables were compared using the χ^2 or Fisher's exact test. All analyses were conducted using the Statistical Package for the Social Sciences (V.17.0; SPSS Institute). A two-sided p value <0.05 was considered to be statistically significant.

RESULTS

In our series of 40 FPC families, DNA analyses were carried out in 28 families (70%). Of the remaining 12 families, DNA was not available. Twenty-seven of the 28 analysed families (96%) were of Caucasian descent and one family (3.6%) was of Indonesian descent (Maluku Islands). These 28 FPC families had a total of 74 affected patients with PC. In 14 families (50%) two family

members were diagnosed with PC, in 12 families (43%) three family members were diagnosed with PC, in one family (3.6%) four family members were diagnosed with PC and in one family (3.6%) seven family members were diagnosed with PC. Of the 74 PC cases, 41 (55%) were male subjects. The mean age of diagnosis of PC was 59.0 years (range 30–84 years, SD 12.3). Nine patients (12%) were younger than 45 at the time of diagnosis. In addition to the PC cases, 24 families (86%) were affected by other types of cancer. Four families (14%) were affected by melanomas, and nine families (32%) were affected by breast cancer.

In 21 FPC families (75%), DNA was available from affected PC cases, isolated from blood samples in 19 families and from PC tumour tissue in two families. In the remaining families, DNA analyses were carried out in DNA of healthy FDR (six families; mean number of FDR tested 1.7, range 1–3) or suspected carriers (one family) because of their position in the pedigree.

DNA analyses of mutations in *CDKN2A/CDK4* led to the identification of a causal genetic factor in six (21.4%) FPC families. In three (50%) of these *CDKN2A*-mutation-positive FPC families, no melanomas and/or dysplastic nevi had been reported at the time of DNA analyses. In the other three *CDKN2A*-mutation-positive FPC families, two had one family member diagnosed with melanoma and in the third family two second degree members were diagnosed with melanoma.

Two different *CDKN2A*-mutations were found, the Dutch founder mutation p16-Leiden (c.225_243del, p.Ala76fs) and the c.19_23dup.p.Ser8fs-mutation. The p16-Leiden-mutation was found in all three melanoma-positive (100%) families and in two of the melanoma-negative (67%) families.

Table 1A shows the characteristics of the *CDKN2A*-mutation-positive FPC families without melanomas; supplementary figures A to C display the pedigrees. These three families included a total of eight PC cases of whom five were male subjects (63%) and the mean age at the time of diagnosis was 51.5 years (SD 9.2). Two patients (25%) were younger than 45 years at the time of diagnosis. The Dutch founder mutation was found in two Caucasian families. The c.19_23dup.p.Ser8fs-mutation was found in the family of Indonesian descent.

The *CDKN2A*-mutation-positive FPC families without melanoma (table 1A) and with melanomas (table 1B) included a total of 19 PC cases of whom 10 were male subjects (53%) and the mean age at the time of diagnosis was 55.7 (SD 10.2). These characteristics were not statistically significantly different from the PC cases of the other FPC families: mean age at the time of diagnosis was 60.1 (SD 12.8), 56% were male persons.

DISCUSSION

In six out of 28 FPC families tested, we identified a *CDKN2A*-mutation (21%), in three of whom (50%) no melanomas and/or dysplastic nevi had been reported at the time of DNA analysis. If the current recommendation would have been followed to test only for *CDKN2A*-mutations in FPC families with at least one melanoma case, these three families would have gone unnoticed.¹⁰ This recommendation is based on three previous studies on the role of *CDKN2A*-mutations in FPC families, which failed to identify *CDKN2A*-mutations in non-melanoma FPC families^{9 12 13} (table 2). Recently, the prevalence of *CDKN2A*-mutations in a large series of unselected PC cases was studied and this turned out to be low (0.6%).¹⁶ A subanalysis of this series in which only FPC cases were included showed *CDKN2A*-mutations in 3.3% of cases. The discrepancy between these and our series is not readily explained, although the method of patient selection between our series (gathered from PC family registries) and the latter large series (unselected PC cases) may account for part of the discrepancy. It

Table 1 Characteristics of *CDKN2A*-positive FPC families without melanomas (A) and *CDKN2A*-positive FPC families with melanomas not fulfilling diagnostic criteria of familial CMM (B)

	No. of family members with PC/gender and age at diagnosis (years)	No. of family members with melanoma	Other tumour types*	Type of mutation
A				
1	3/♂48, ♂55, ♂67 (supplementary figure A)	0	Lung cancer n=1	c.19_23dup.p.Ser8fs
2	3/♂39, ♀41, ♀52 (supplementary figure B)	0	Cancer unknown origin n=2	c.225_243del, p.Ala76fs
3	2/♀51, ♂59 (supplementary figure C)	0†	Basal cell carcinoma n=1	c.225_243del, p.Ala76fs
B				
4	2/♂50, ♀67	1	Pharyngeal cancer n=1‡ Gastric cancer n=1‡	c.225_243del, p.Ala76fs
5	2/♂62, ♂73	1	No	c.225_243del, p.Ala76fs
6	7/♀50, ♂50, ♂51, ♀59, ♀65, ♀74, ♀76	2	Prostate cancer n=1 Thyroid cancer n=1	c.225_243del, p.Ala76fs

*Other associated tumour types in family.

†After disclosure of the *CDKN2A*-mutation in this family, a melanoma was diagnosed at dermatological surveillance in a 17-year-old female family member.

‡Same patient.

CMM, cutaneous malignant melanoma; FPC, familial PC; PC, pancreatic cancer.

does not seem likely that the differences in results can be explained by the type of *CDKN2A*-mutations that we found. The Dutch founder mutation p16-Leiden, which two of our *CDKN2A*-mutation-positive non-melanoma FPC families carried, is a well-researched mutation; the phenotype of its carriers is not restricted to clustering of PC only.³ Although, a part of the differences might be explained by the founder role of this mutation. The third *CDKN2A*-mutation-positive non-melanoma FPC family carried a c.19_23dup.p.Ser8fs-mutation. To our knowledge, this is a new mutation that has not been previously reported. The frame shift that is caused by this mutation causes a stop-codon. Based on the results of this one family, it is too early to claim that this specific mutation causes a phenotype without melanomas. The family in whom the c.19_23dup.p.Ser8fs-mutation was detected is of Indonesian descent and their darker-skinned complexion might have offered them added protection from developing melanomas. It is well known that the risk of developing melanoma is higher in fair-skinned people, especially those with blond or red hair and who sunburn and freckle easily than in people with darker complexions.¹⁷ The two families with the Dutch founder mutation were Caucasian.

Table 2 Overview of literature on the role of *CDKN2A*-mutations in FPC

Study	Study population	<i>CDKN2A</i> -mutation found	Type(s) of mutation	Phenotype
Slater <i>et al</i> ¹³	56 FPC families	No	—	—
Bartsch <i>et al</i> ⁹	18 FPC families	No	—	—
Moskaluk <i>et al</i> ¹²	21 FPC families	Yes	c.457 G>T	Mel-PC family*
Current study	28 FPC families	Yes	c.19_23dup.p.Ser8fs	FPC family
			c.225_243del, p.Ala76fs	FPC family
			c.225_243del, p.Ala76fs	FPC family†
			c.225_243del, p.Ala76fs	Mel-PC family*
			c.225_243del, p.Ala76fs	Mel-PC family*
			c.225_243del, p.Ala76fs	Mel-PC family*

*Family affected by PC and melanoma but that does not fulfil the diagnostic criteria of familial cutaneous malignant melanoma.

†After disclosure of the *CDKN2A* mutation, a melanoma was diagnosed in this family. FPC, familial PC; PC, pancreatic cancer.

Differences in lifestyle may also explain some of the difference between the results of earlier studies and our series. For example, it is well known that cigarette smoking is associated with an increased risk of PC.¹⁸ Unfortunately, we lack detailed information about smoking status. We therefore cannot exclude the possibility that in our series the PC affected family members of non-melanoma *CDKN2A*-mutation-positive families smoked more than affected individuals in the previously published studies which also did not report on smoking status.

Another limitation of this current series is that in some families affected relatives were unavailable for DNA testing and, instead, unaffected FDRs were tested. A negative genetic test result in such cases does not exclude the presence of a pathogenic mutation unless a specific genetic mutation is been found in another relative. This may have caused an underestimation of the prevalence of *CDKN2A/CDK4* in this current study.

We were able to collect detailed information on the family history of all FPC families in whom DNA analyses were carried out. In addition, patients not known with any skin lesions before they were genetically tested were seen by a dermatologist, minimising the chance that we missed a diagnosis of melanoma or dysplastic nevi negligible. Since in both family B and family C some family members died of cancer of unknown origin, we cannot state with 100% certainty that none of these individuals died of melanoma.

The three non-melanoma FPC families in which a *CDKN2A*-mutation was found were of moderate to large size. It is therefore less likely that melanoma or dysplastic nevi were not observed because of a low a priori chance based on numbers and RR. Interestingly, during dermatological follow-up of one of our *CDKN2A*-positive FPC families we detected an early stage melanoma in a 17-year-old female family member. A year after resection of a 5-mm superficial spreading melanoma (Breslow 0.8 mm), this patient is disease-free.

Among the 28 families in which *CDKN2A*-mutation was performed, four families (14%) were affected by ≥1 melanoma (s). It is of interest that in three (75%) of these melanoma-positive families, a mutation in *CDKN2A* was found. These findings are in line with previous reports showing that *CDKN2A*-mutations are frequently found in families affected by both PC and melanomas.⁸⁻⁹ The prevalence of *CDKN2A*-mutations in the remaining melanoma-negative FPC families was 12%.

A number of previous reports have shown an indication for *BRCA2*-mutation analysis in FPC families that did not meet the criteria of familial breast and ovarian cancer.^{19–21} In a similar way, our findings emphasise the need to include *CDKN2A*-mutation analysis in genetic testing for FPC families, even in the absence of reported melanomas. It will help to better identify those at risk of developing PC and/or melanoma.

Surveillance of individuals at a high risk of malignant melanomas has proved to lead to early detection of melanomas and will consequently have a favourable effect in prognosis.^{22–24} Surveillance of individuals at high risk of PC is emerging and may lead to an improvement of prognosis and a decline in PC incidence.^{25–30}

In conclusion, the results of this series show that *CDKN2A*-mutation can be found in a considerable proportion of families with FPC. *CDKN2A*-mutation analysis should therefore be included in genetic testing in FPC families, even in the absence of reported melanomas. This strategy will enhance the recognition of individuals at risk for PC and facilitate the early detection of melanomas.

Acknowledgements On behalf of the Dutch Research Group of Pancreatic Cancer Surveillance in High-Risk Individuals (in alphabetical order) Amsterdam Medical Center: Cora M Aalfs, Marcel GW Dijkgraaf, Paul Fockens, Dirk J Gouma, Jeanin E van Hooft, C Yung Nio, Theo AM van Os, Ellen MA Smets. Erasmus Medical Center: Katharina Biermann, Marco J Bruno, Casper HJ van Eijck, Femme Harinck, Nanda Krak, Jan- Werner Poley, Anja Wagner. The Netherlands Cancer Institute: Eveline MA Bleiker, Annemieke Cats, Irma Kluij, Anja van Rens, Grace Sidharta, Senno Verhoef. University Medical Center Groningen: Hendrik M van Dullemen, Rolf H Sijmons).

Contributors MJB supervised the study, was responsible for study concept and design, the acquisition of the data, the analysis and interpretation of the data and was responsible for drafting of the manuscript. FH was responsible for acquisition of the data, the analysis and interpretation of the data and was responsible for drafting of the manuscript. TAMVO and IK were responsible for the genetic counselling of patients, were responsible for acquisition of the data, the analysis and interpretation of the data and were responsible for drafting of the manuscript. RO, AW, CMA, RHS were responsible for the genetic counselling of patients and helped with the critical revision of the manuscript for important intellectual content. NvdS performed the *CDKN2A/CDK4*-mutation analysis and helped with the critical revision of the manuscript for important intellectual content. J-WP, EJK and PF helped with the critical revision of the manuscript for important intellectual content. All authors have approved the final draft submitted.

Competing interests None.

Ethics approval Approval provided by the Ethics Committee Erasmus MC, Ethics Committee AMC, Ethics Committee NKI/AVL, Ethics Committee UMCG.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

- Lynch HT, Smyrk T, Kern SE, Hruban RH, Lightdale CJ, Lemon SJ, Lynch JF, Fusaro LR, Fusaro RM, Ghadirian P. Familial pancreatic cancer: a review. *Semin Oncol* 1996;**23**:251–75.
- Goldstein AM, Chan M, Harland M, Gillanders EM, Hayward NK, Avril MF, Azizi E, Bianchi-Scarra G, Bishop DT, Bressac-de Paillerets B, Bruno W, Calista D, Cannon Albright LA, Demenais F, Elder DE, Ghiorzo P, Gruis NA, Hansson J, Hogg D, Holland EA, Kanetsky PA, Kefford RF, Landi MT, Lang J, Leachman SA, Mackie RM, Magnusson V, Mann GJ, Niendorf K, Newton Bishop J, Palmer JM, Puig S, Puig-Butlle JA, de Snoo FA, Stark M, Tsao H, Tucker MA, Whitaker L, Yakobson E. High-risk melanoma susceptibility genes and pancreatic cancer, neural system tumors, and uveal melanoma across GenoMEL. *Cancer Res* 2006;**66**:9818–28.
- de Snoo FA, Bishop DT, Bergman W, van Leeuwen I, van der Drift C, van Nieuwpoort FA, Out-Luiting CJ, Vasen HF, ter Huurne JA, Frants RR, Willemze R, Breuning MH, Gruis NA. Increased risk of cancer other than melanoma in *CDKN2A* founder mutation (p16-Leiden)-positive melanoma families. *Clin Cancer Res* 2008;**14**:7151–7.
- Borg A, Sandberg T, Nilsson K, Johannsson O, Klinker M, Masback A, Westerdahl J, Olsson H, Ingvar C. High frequency of multiple melanomas and breast and pancreas carcinomas in *CDKN2A* mutation-positive melanoma families. *J Natl Cancer Inst* 2000;**92**:1260–6.
- Online Mendelian Inheritance in Man. Baltimore, MD: Johns Hopkins University. MIM Number: 155600. <http://omim.org/> (accessed 7 Jul 2011).
- Gruis NA, Sandkuijl LA, van der Velden PA, Bergman W, Frants RR. *CDKN2* explains part of the clinical phenotype in Dutch familial atypical multiple-mole melanoma (FAMMM) syndrome families. *Melanoma Res* 1995;**5**:169–77.
- Goldstein AM, Chan M, Harland M, Hayward NK, Demenais F, Bishop DT, Azizi E, Bergman W, Bianchi-Scarra G, Bruno W, Calista D, Albright LA, Chaudru V, Chompret A, Cuellar F, Elder DE, Ghiorzo P, Gillanders EM, Gruis NA, Hansson J, Hogg D, Holland EA, Kanetsky PA, Kefford RF, Landi MT, Lang J, Leachman SA, Mackie RM, Magnusson V, Mann GJ, Bishop JN, Palmer JM, Puig S, Puig-Butlle JA, Stark M, Tsao H, Tucker MA, Whitaker L, Yakobson E; Lund Melanoma Study Group; Melanoma Genetics Consortium (GenoMEL). Features associated with germline *CDKN2A* mutations: a GenoMEL study of melanoma-prone families from three continents. *J Med Genet* 2007;**44**:99–106.
- Bartsch DK, Langer P, Habbe N, Matthai E, Chaloupka B, Sina M, Hahn SA, Slater EP. Clinical and genetic analysis of 18 pancreatic carcinoma/melanoma-prone families. *Clin Genet* 2010;**77**:333–41.
- Bartsch DK, Sina-Frey M, Lang S, Wild A, Gerdes B, Barth P, Kress R, Grutzmann R, Colombo-Benkmann M, Ziegler A, Hahn SA, Rothmund M, Rieder H. *CDKN2A* germline mutations in familial pancreatic cancer. *Ann Surg* 2002;**236**:730–7.
- Brand RE, Lerch MM, Rubinstein WS, Neoptolemos JP, Whitcomb DC, Hruban RH, Brentnall TA, Lynch HT, Canto MI. Advances in counselling and surveillance of patients at risk for pancreatic cancer. *Gut* 2007;**56**:1460–9.
- Lynch HT, Brand RE, Lynch JF, Fusaro RM, Smyrk TC, Goggins M, Kern SE. Genetic counseling and testing for germline p16 mutations in two pancreatic cancer-prone families. *Gastroenterology* 2000;**119**:1756–60.
- Moskaluk CA, Hruban H, Lietman A, Smyrk T, Fusaro L, Fusaro R, Lynch J, Yeo CJ, Jackson CE, Lynch HT, Kern SE. Novel germline p16(INK4) allele (Asp145Cys) in a family with multiple pancreatic carcinomas. Mutations in brief no. 148. Online. *Hum Mutat* 1998;**12**:70.
- Slater EP, Langer P, Fendrich V, Habbe N, Chaloupka B, Matthai E, Sina M, Hahn SA, Bartsch DK. Prevalence of *BRCA2* and *CDKN2A* mutations in German familial pancreatic cancer families. *Fam Cancer* 2010;**9**:335–43.
- Whelan AJ, Bartsch D, Goodfellow PJ. Brief report: a familial syndrome of pancreatic cancer and melanoma with a mutation in the *CDKN2* tumor-suppressor gene. *N Engl J Med* 1995;**333**:975–7.
- OncoLine Cancer Clinical Practice Guidelines. Vereniging van Integrale Kankercentra the Netherlands. <http://oncoline.nl/fammm> (accessed 1 Jul 2011).
- McWilliams RR, Wieben ED, Rabe KG, Pedersen KS, Wu Y, Sciotte H, Petersen GM. Prevalence of *CDKN2A* mutations in pancreatic cancer patients: implications for genetic counseling. *Eur J Hum Genet* 2011;**19**:472–8.
- Marrett LD, King WD, Walter SD, From L. Use of host factors to identify people at high risk for cutaneous malignant melanoma. *CMAJ* 1992;**147**:445–53.
- Fuchs CS, Colditz GA, Stampfer MJ, Giovannucci EL, Hunter DJ, Rimm EB, Willett WC, Speizer FE. A prospective study of cigarette smoking and the risk of pancreatic cancer. *Arch Intern Med* 1996;**156**:2255–60.
- Murphy KM, Brune KA, Griffin C, Sollenberger JE, Petersen GM, Bansal R, Hruban RH, Kern SE. Evaluation of candidate genes *MAP2K4*, *MADH4*, *ACVR1B*, and *BRCA2* in familial pancreatic cancer: deleterious *BRCA2* mutations in 17%. *Cancer Res* 2002;**62**:3789–93.
- Hahn SA, Greenhalf B, Ellis I, Sina-Frey M, Rieder H, Korte B, Gerdes B, Kress R, Ziegler A, Raeburn JA, Campa D, Grutzmann R, Rehder H, Rothmund M, Schmiegel W, Neoptolemos JP, Bartsch DK. *BRCA2* germline mutations in familial pancreatic carcinoma. *J Natl Cancer Inst* 2003;**95**:214–21.
- Couch FJ, Johnson MR, Rabe KG, Brune K, de Andrade M, Goggins M, Rothenmund H, Gallinger S, Klein A, Petersen GM, Hruban RH. The prevalence of *BRCA2* mutations in familial pancreatic cancer. *Cancer Epidemiol Biomarkers Prev* 2007;**16**:342–6.
- Vasen HF, Bergman W, van Haeringen A, Scheffer E, van Slooten EA. The familial dysplastic nevus syndrome. Natural history and the impact of screening on prognosis. A study of nine families in the Netherlands. *Eur J Cancer Clin Oncol* 1989;**25**:337–41.
- Rhodes AR, Weinstock MA, Fitzpatrick TB, Mihm MC Jr, Sober AJ. Risk factors for cutaneous melanoma. A practical method of recognizing predisposed individuals. *JAMA* 1987;**258**:3146–54.
- Masri GD, Clark WH Jr, Guerry D 4th, Halpern A, Thompson CJ, Elder DE. Screening and surveillance of patients at high risk for malignant melanoma result in detection of earlier disease. *J Am Acad Dermatol* 1990;**22**:1042–8.
- Canto MI, Goggins M, Hruban RH, Petersen GM, Giardiello FM, Yeo C, Fishman EK, Brune K, Axilbund J, Griffin C, Ali S, Richman J, Jagannath S, Kantsevov SV, Kallou AN. Screening for early pancreatic neoplasia in high-risk individuals: a prospective controlled study. *Clin Gastroenterol Hepatol* 2006;**4**:766–81; quiz 665.
- Kimmey MB, Bronner MP, Byrd DR, Brentnall TA. Screening and surveillance for hereditary pancreatic cancer. *Gastrointest Endosc* 2002;**56**:S82–6.
- Langer P, Kann PH, Fendrich V, Habbe N, Schneider M, Sina M, Slater EP, Heverhagen JT, Gress TM, Rothmund M, Bartsch DK. Five years of prospective screening of high-risk individuals from families with familial pancreatic cancer. *Gut* 2009;**58**:1410–18.
- Poley JW, Kluij I, Gouma DJ, Harinck F, Wagner A, Aalfs C, van Eijck CH, Cats A, Kuipers EJ, Nio Y, Fockens P, Bruno MJ. The yield of first-time endoscopic ultrasonography in screening individuals at a high risk of developing pancreatic cancer. *Am J Gastroenterol* 2009;**104**:2175–81.
- Vasen HF, Wasser M, van Mil A, Tollenaar RA, Konstantinovskii M, Gruis NA, Bergman W, Hes FJ, Hommes DW, Offerhaus GJ, Morreau H, Bonsing BA, de Vos tot Nederveen Cappel WH. Magnetic resonance imaging surveillance detects early-stage pancreatic cancer in carriers of a p16-Leiden mutation. *Gastroenterology* 2011;**140**:850–6.
- Verna EC, Hwang C, Stevens PD, Rotterdam H, Stavropoulos SN, Sy CD, Prince MA, Chung WK, Fine RL, Chabot JA, Frucht H. Pancreatic cancer screening in a prospective cohort of high-risk patients: a comprehensive strategy of imaging and genetics. *Clin Cancer Res* 2010;**16**:5028–37.

Indication for *CDKN2A*-mutation analysis in familial pancreatic cancer families without melanomas

Femme Harinck, Irma Kluijt, Nienke van der Stoep, et al.

J Med Genet 2012 49: 362-365 originally published online May 25, 2012

doi: 10.1136/jmedgenet-2011-100563

Updated information and services can be found at:

<http://jmg.bmj.com/content/49/6/362.full.html>

These include:

Data Supplement

"Supplementary Data"

<http://jmg.bmj.com/content/suppl/2012/05/24/jmedgenet-2011-100563.DC1.html>

References

This article cites 28 articles, 11 of which can be accessed free at:

<http://jmg.bmj.com/content/49/6/362.full.html#ref-list-1>

Email alerting service

Receive free email alerts when new articles cite this article. Sign up in the box at the top right corner of the online article.

Topic Collections

Articles on similar topics can be found in the following collections

[Cancer: dermatological](#) (38 articles)
[Dermatology](#) (220 articles)
[Screening \(oncology\)](#) (207 articles)
[Pancreas and biliary tract](#) (100 articles)

Notes

To request permissions go to:

<http://group.bmj.com/group/rights-licensing/permissions>

To order reprints go to:

<http://journals.bmj.com/cgi/reprintform>

To subscribe to BMJ go to:

<http://group.bmj.com/subscribe/>