Melanoma cutaneo ereditario

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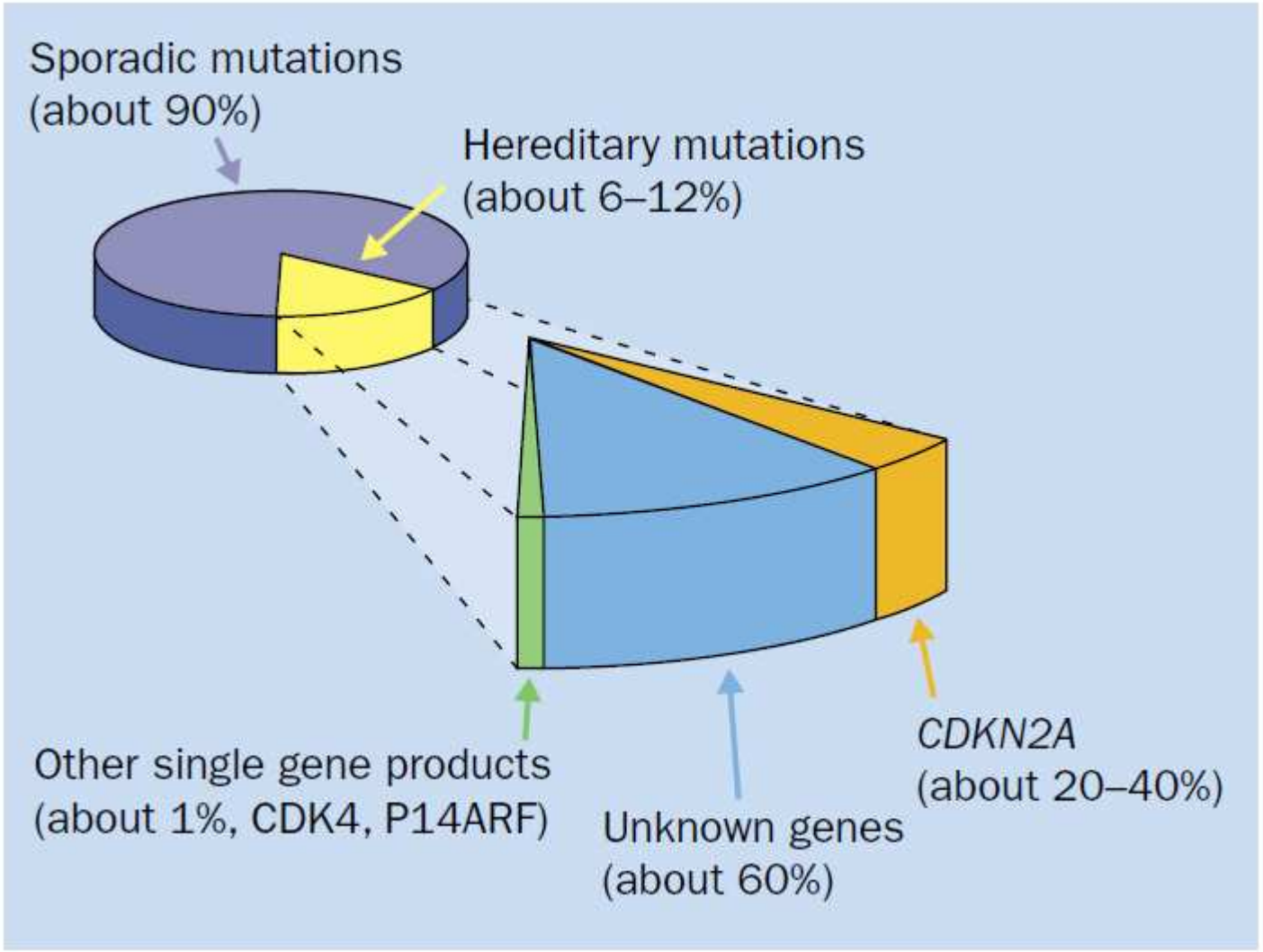
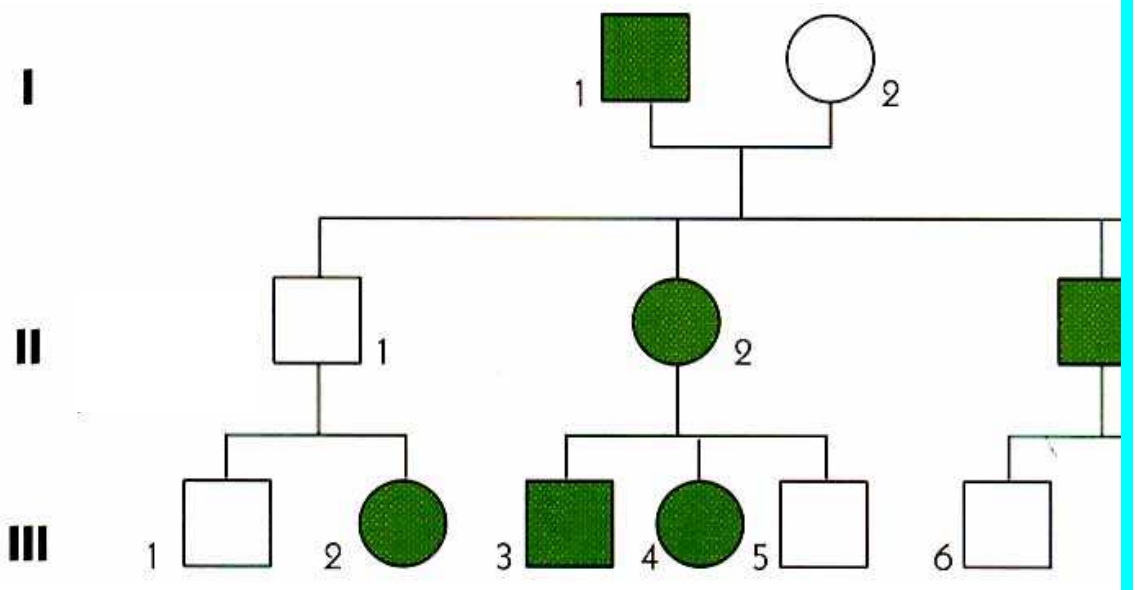
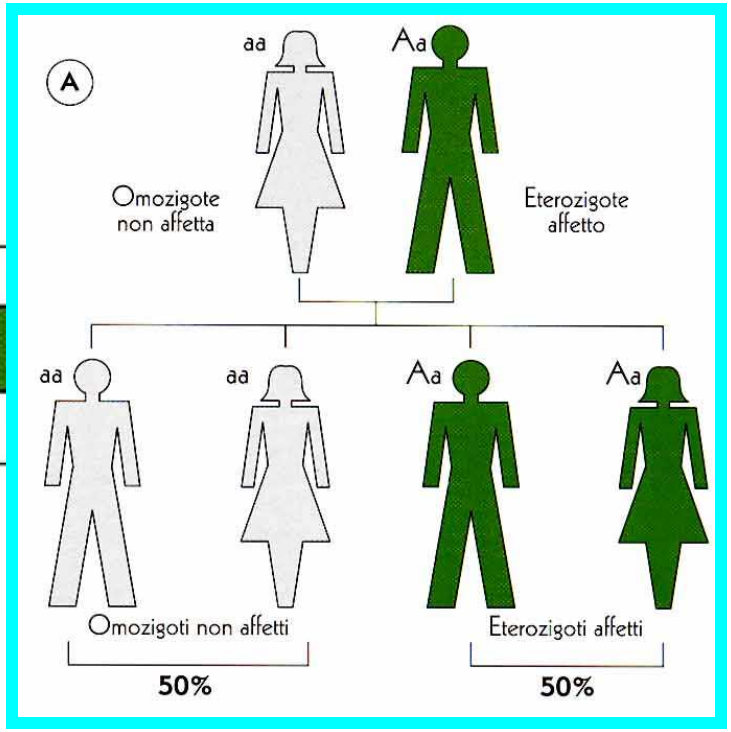

Sporadic mutations
(about 90%)
Hereditary mutations
(about 6–12%)
Other single gene products
(about 1%, CDK4, P14ARF)
Unknown genes
(about 60%)
CDKN2A
(about 20–40%)





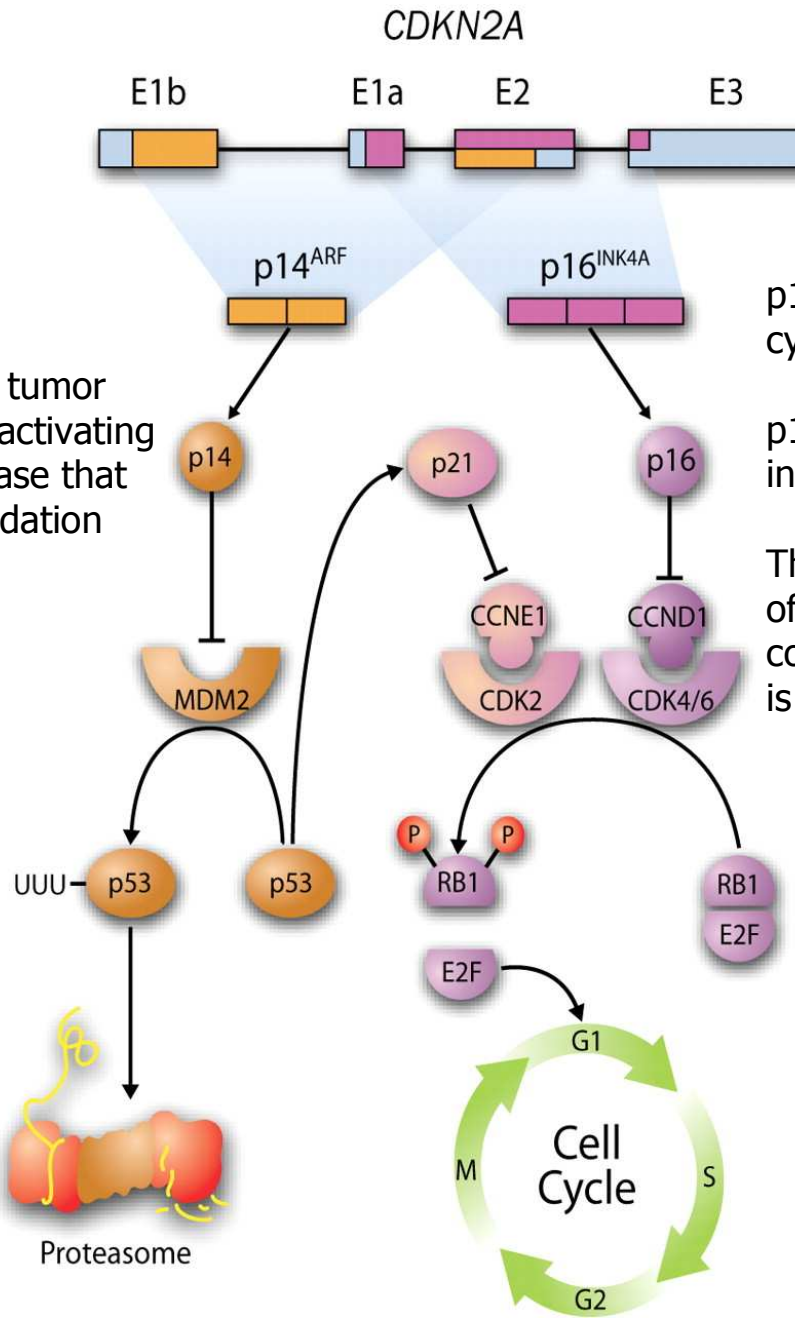
In una parte degli alberi genealogici di melanoma familiare, il pattern di segregazione è suggestivo di una trasmissione autosomica dominante
con penetranza incompleta e espressività variabile.

CDKN2A
(Cyclin-dependent kinase inhibitor 2A)
9p21

- Clonato nel 1994; originariamente denominato **MTS1** (Multiple Tumor Suppressor –1)
- Alta frequenza di delezioni in omozigosi in linee cellulari derivanti da melanomi, tumori del polmone, mammella, SNC, ossa, vescica, rene, ovaio e leucemie

Kamb, A. et al A cell cycle regulator potentially involved in genesis of many tumor types. *Science* 1994

p14ARF activates the tumor Suppressor p53 by inactivating HDM2, a ubiquitin ligase that targets p53 for degradation by the proteasome



p16 belongs to the family of cyclin-dependent kinase (Cdk) inhibitors

p16 activation causes cell cycle arrest in G1 phase

This happens following the interaction of p16 with CdK4 and Cdk6; consequently, Rb phosphorylation is inhibited.

ORIGINAL ARTICLE

Features associated with germline CDKN2A mutations: a GenoMEL study of melanoma-prone families from three continents

J Med Genet 2007;**44**:99–106.

385 famiglie con ≥ 3 casi di melanoma (Nord America, Europa, Australia)

Frequenza di mutazioni di *CDKN2A*: 39%

20% in Australia

45% in Nord America

57% in Europa

Detection rate correlata con:

1) n° di casi in famiglia

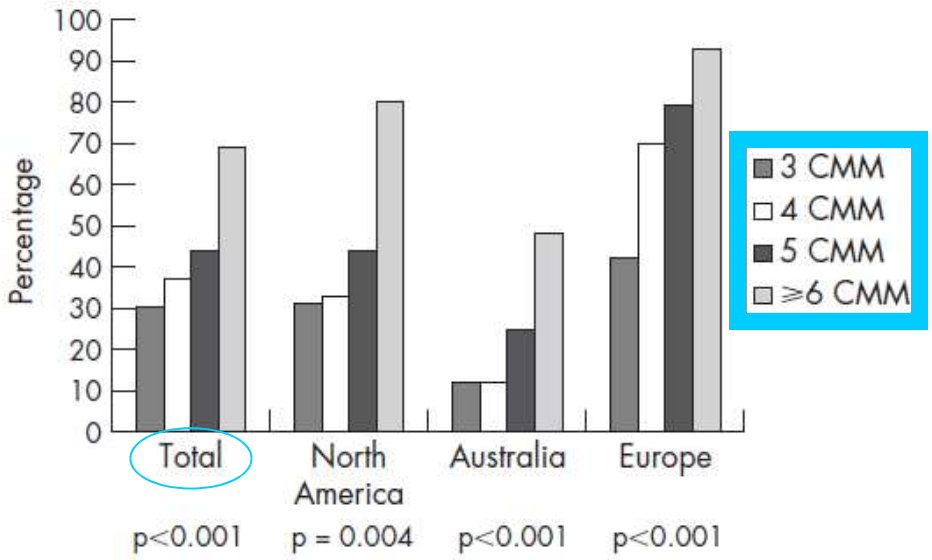


Figure 1 Percentage of families with CDKN2A mutations by number of patients with cutaneous malignant melanoma per family (no. of CMM/family: 3, 4, 5 and ≥6) for each of the four groups (total, North America, Australia and Europe). p Values are shown for each of the four groups.

Detection rate correlata con:

2) presenza di pz. con melanoma multiplo

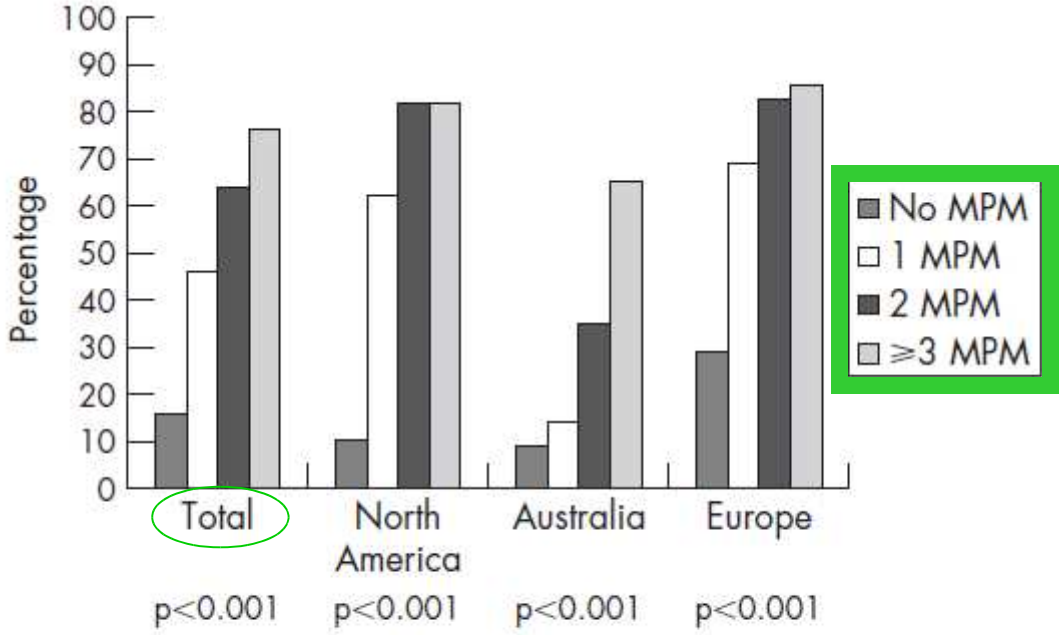


Figure 2 Percentage of families with CDKN2A mutations by number of patients with multiple primary melanoma (MPM: 0, 1, 2 and ⩾3) in a family for each of the four groups (total, North America, Australia and Europe). p Values are shown for each of the four groups.

Detection rate correlata con:

3) età precoce alla diagnosi

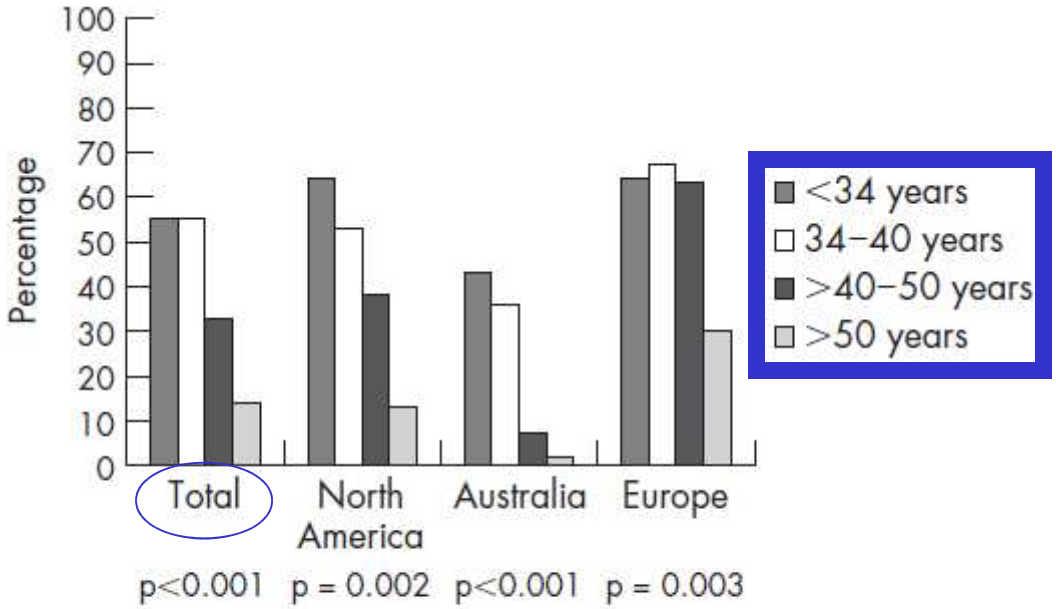


Figure 4 Percentage of families with CDKN2A mutations by median age (in years) at melanoma diagnosis (MedAge: <34, 34–40, >40–50 and >50 years) in a family for each of the four groups (total, North America, Australia and Europe). p Values are shown for each of the four groups.

ORIGINAL ARTICLE

Clinical genetic testing for familial melanoma in Italy: A cooperative study

William Bruno, MD, PhD,[a*] Paola Ghiorzo, PhD,[a*] Linda Battistuzzi, MS,[a*] Paolo A. Ascierto, MD,[b] Monica Barile, MD,[c] Sara Gargiulo, PhD,[a] Francesca Gensini, MD,[d] Sara Gliori, MD,[a] Michele Guida, MD,[e] Maurizio Lombardo, MD,[f] Siranoush Manoukian, MD,[g] Chiara Menin, PhD,[h] Sabina Nasti, PhD,[a] Paola Origone, PhD,[a] Barbara Pasini, MD,[i] Lorenza Pastorino, PhD,[a] Bernard Peissel, MD,[g] Maria Antonietta Pizzichetta, MD,[j] Paola Queirolo, MD,[k] Monica Rodolfo, PhD,[g] Antonella Romanini, MD,[l] Maria Chiara Scaini, PhD,[m] Alessandro Testori, MD,[n] Maria Grazia Tibiletti, MD,[o] Daniela Turchetti, MD,[p] Sancy A. Leachman, MD,[q] and Giovanna Bianchi Scarrà, PhD,[a] on behalf of IMI, the Italian Melanoma Intergroup

Genoa, Naples, Milan, Florence, Bari, Varese, Padua, Turin, Aviano, Pisa, and Bologna, Italy; and Salt Lake City, Utah

J Am Acad Dermatol 2009 in press

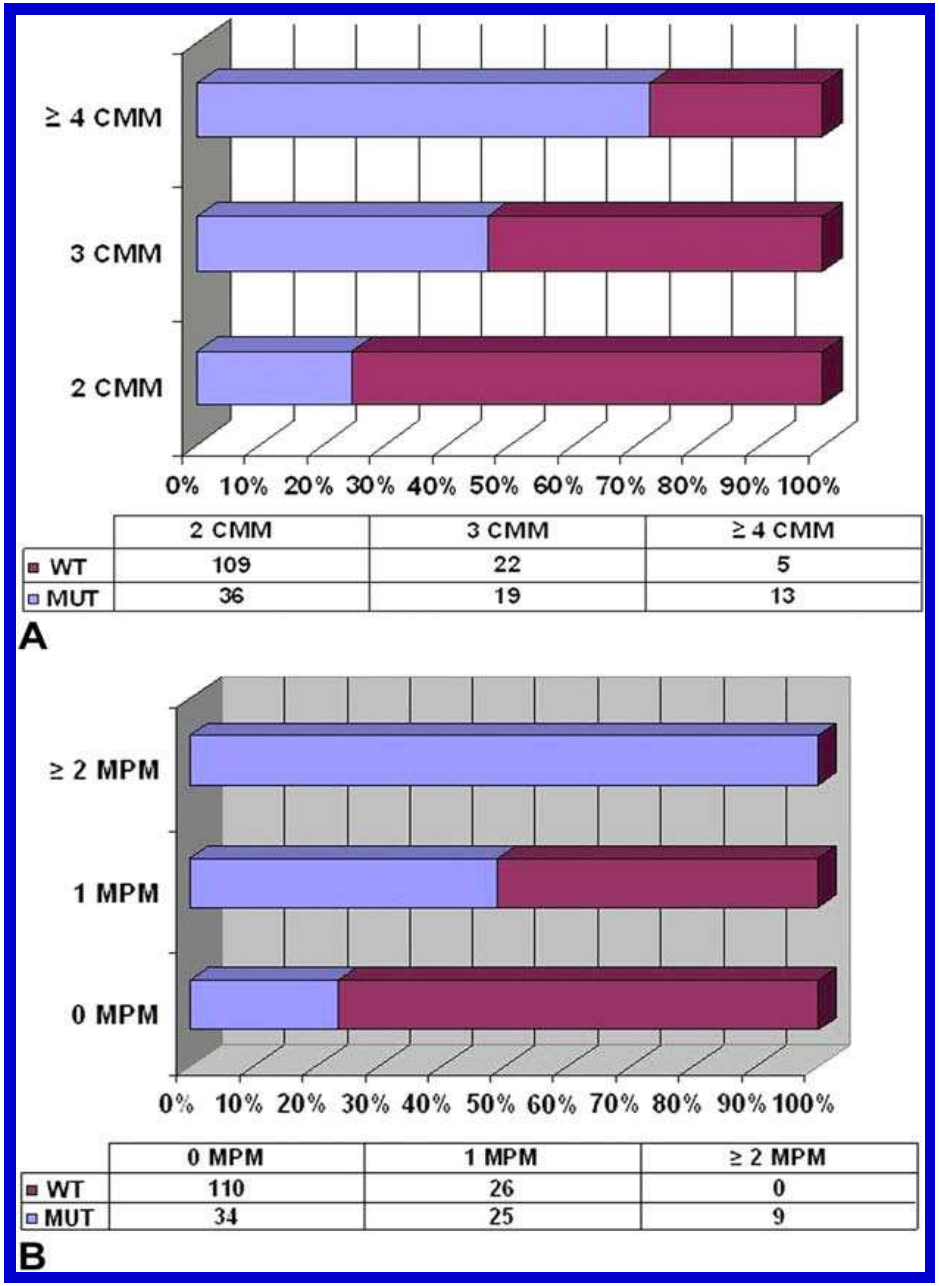
204 famiglie con ≥ 2 soggetti affetti di 9 centri Italiani

Frequenza di mutazioni in *CDKN2A*: 33%

Nelle 145 famiglie con 2 soggetti affetti: 25%

25%> 10% soglia di probabilità stabilita dall'American Society

Of Clinical Oncology per l'accesso ai test genetici per predisposizione oncologica



	2 CMM	3 CMM	≥ 4 CMM
WT	109	22	5
MUT	36	19	13

	0 MPM	1 MPM	≥ 2 MPM
WT	110	26	0
MUT	34	25	9

Fig 3. Cyclin-dependent kinase inhibitor 2A mutation frequency according to number of affected cases (A) and presence of multiple primary melanomas (MPM) (B) in family. CMM, cutaneous malignant melanoma; MUT, mutated; WT, wild-type.

Gene Symbol	Chromosomal location	Gene name	cDNA sequence	Extended cDNA
CDKN2A	9p21	Cyclin-dependent kinase inhibitor 2A (p16)	Get cDNA	BIOBASE Feature available to subscribers

Mutation type	Number of mutations	M
Missense/nonsense	89	
Splicing	11	
Regulatory	3	
Small deletions	12	
Small insertions	8	
Small indels	2	
Gross deletions	6	
Gross insertions	2	
Complex rearrangements	0	
Repeat variations	0	
Public total (HGMD Professional 2009.2 total)	**133** (160)	

Genomic rearrangements of the *CDKN2A* locus are infrequent in Italian malignant melanoma families without evidence of *CDKN2A/CDK4* point mutations

Marina Vignoli[a], Maria Chiara Scaini[b], Paola Ghiorzo[c], Roberta Sestini[d], William Bruno[c], Chiara Menin[e], Francesca Gensini[d], Mauro Piazzini[d], Alessandro Testori[f], Siranoush Manoukian[g], Claudio Orlando[h], Emma D'Andrea[b,e], Giovanna Bianchi-Scarrà[c] and Maurizio Genuardi[a,d]

Melanoma Research 2008, 18:431–437

124 famiglie di 5 centri Italiani

In conclusion, since large deletions involving *CDKN2A* are rare, routine search for these rearrangements in *CDKN2A*- and *CDK4*-mutation negative CMM families does not seem to be warranted, although it would be reasonable to pursue it in selected cases with very strong family history and/or showing linkage to 9p21.

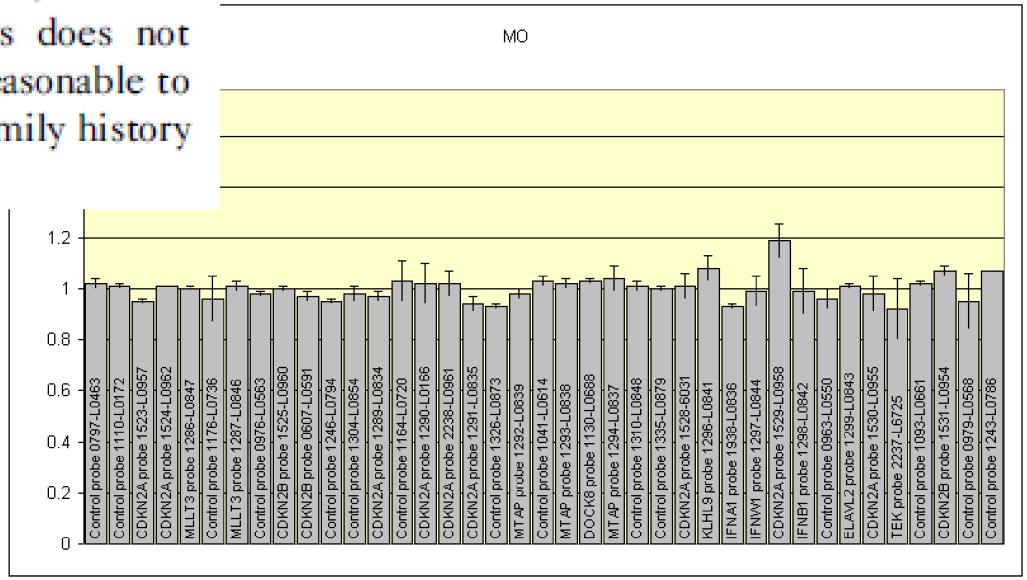
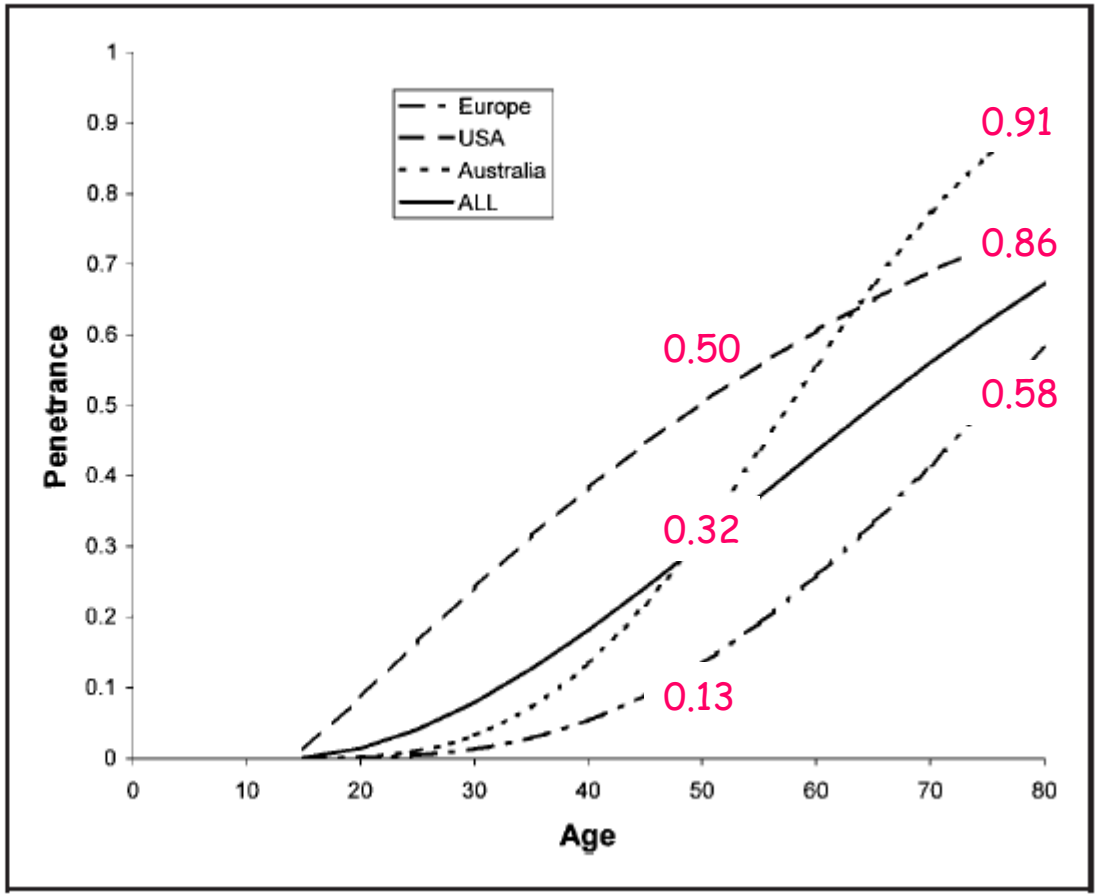


Fig. 1. Estimated age-specific penetrance estimates for CDKN2A mutations. Penetrances are shown for the total set of families in the study, assuming the same penetrance of mutations in all geographic locations (ALL); families living in Australia (Australia); families living in France, Italy, The Netherlands, or the United Kingdom (Europe); and families living in the United States (USA).



→ 0.30 a 50aa
→ 0.67 a 80aa

Geographical Variation in the Penetrance of CDKN2A Mutations for Melanoma

Bishop DT et al. J Natl Cancer Inst 2002

Familial Atypical Melanotic Mole Melanoma (FAMMM)

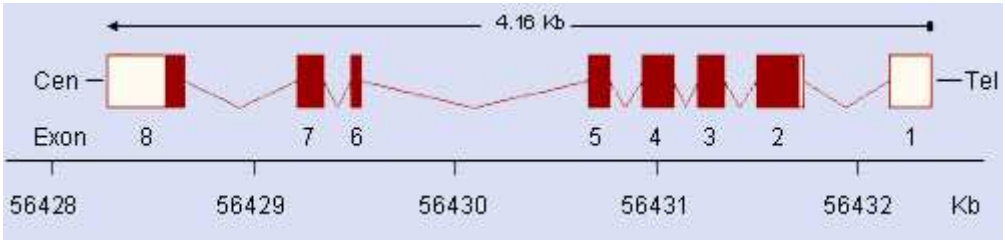
All of the following criteria:

1. Malignant melanoma in one or more first- or second-degree relatives
2. High total body nevi count (often >50) including some of which are clinically atypical
3. Nevi with certain histologic features on microscopy

25-40% with *CDKN2A* mutation		60-75% without *CDKN2A* mutation
60-90% melanoma by age 80 17% pancreatic cancer by age 75		Cancer risks unclear

Altri geni……

CDK4 (cyclin-dependent protein kinase 4)



- cromosoma 12q14

-nel 2% delle famiglie nel GenoMEL (Goldstein 2006)

- < di 15 famiglie descritte nel mondo

-mutazioni più frequenti: Arg24His, Arg24Cys

Table 1 Summary of low-penetrance melanoma susceptibility factors

Gene	Variant	*N* cases	*N* controls	Odds ratio (95% CI)	*P* value	References
MC1R	Val60Leu	1,903	3,162	1.15 (0.92–1.43)	0.01	Raimondi et al. (2008)
	(rs1805005 T)	1,947	11,173	1.13 (1.01–1.26)	0.04	Gudbjartsson et al. (2008)
	Asp84Glu	1,271	1,773	2.40 (1.50–3.84)	0.47	Raimondi et al. (2008)
	(rs1805006 A)	1,936	10,404	1.35 (0.94–1.96)	0.11	Gudbjartsson et al. (2008)
	Val92Met	1,635	2,631	1.22 (0.99–1.50)	0.31	Raimondi et al. (2008)
	(rs2228479 A)	1,965	10,536	1.03 (0.91–1.18)	0.63	Gudbjartsson et al. (2008)
	Arg142His	1,098	1,614	1.66 (1.01–2.75)	0.46	Raimondi et al. (2008)
R	Arg151Cys	1,905	3,142	1.78 (1.45–2.20)	0.25	Raimondi et al. (2008)
	(rs1805007 T)	1,970	12,237	1.47 (1.28–1.70)	1.4×10^{-7}	Gudbjartsson et al. (2008)
	Ile155Thr	1,021	1,929	2.45 (1.32–4.55)	0.37	Raimondi et al. (2008)
	(rs1110400 C)	1,963	10,756	1.10 (0.78–1.55)	0.6	Gudbjartsson et al. (2008)
R	Arg160Trp	1,900	3,164	1.43 (1.20–1.70)	0.64	Raimondi et al. (2008)
	(1805008 T)	1,950	11,837	1.26 (1.12–1.41)	1.1×10^{-4}	Gudbjartsson et al. (2008)
	Arg163Gln	1,617	2,730	1.42 (1.09–1.85)	0.36	Raimondi et al. (2008)
	(rs885479 A)	2,093	38,633	1.05 (0.89–1.22)	0.58	Gudbjartsson et al. (2008)
R	Asp294His	1,657	2,816	1.77 (1.17–2.69)	0.08	Raimondi et al. (2008)
	(rs1805009 C)	1,961	10,699	1.68 (1.28–2.22)	2.2×10^{-4}	Gudbjartsson et al. (2008)
ASIP	rs1015362 G; rs4911414 T	2,111	40,094	1.45 (1.29–1.64)	1.2×10^{-9}	Gudbjartsson et al. (2008)
	rs910873; rs1885120	2,019	2,105	1.75 (1.53–2.01)	1.0×10^{-15}	Brown et al. (2008)
TYR	Arg402Gln (rs1126809 A)	2,111	40,599	1.21 (1.13–1.30)	2.8×10^{-7}	Gudbjartsson et al. (2008)
TYRP1	rs1408799 C	2,110	40,043	1.15 (1.06–1.24)	4.3×10^{-4}	Gudbjartsson et al. (2008)

Hum Genet
DOI 10.1007/s00439-009-0715-9

REVIEW ARTICLE

Genetic risk factors for melanoma

Kathrine Damm Meyle · Per Guldberg

Published online: 8 July 2009

Gene-gene interaction *CDKN2A/MC1R*

In the Australian cohort co-inheritance of a *MC1R* variant Increased the penetrance of *CDKN2A* mutations and decreased the mean age of onset
Box et al , Am J Hum Genet 2001

In the Dutch cohort the penetrance of p16-Leiden mutation Was increased in carriers of one or two *MC1R* variants (18%→35%→55%)
Van der Velden et al , Am J Hum Genet 2001

Raccomandazioni per consulenza e test genetici nel melanoma ereditario. Gruppo SIGU-ONC

Indicazioni per l'invio alla consulenza genetica oncologica per melanoma familiare

Storia personale o familiare di:

- Mutazione nota in un gene predisponente
- Due o più casi di melanoma nello stesso ramo della famiglia
- Presenza di melanoma multiplo
- Sindrome del nevo displastico (o nevo atipico) e melanoma (nel paziente con DNS o nei familiari)

Colloquio iniziale (pre-test)

Raccolta dei dati personali e familiari (anche altri tipi di tumore)

Vengono illustrati:
-Gli aspetti genetici del melanoma familiare
-L'utilità del test proposto ed i suoi limiti
-Una stima del rischio

Obiettivo:
aiutare i soggetti a rischio genetico a comprendere le opzioni attualmente disponibili e decidere dopo adeguata informazione

Secondo colloquio

Il pz comunica la propria decisione di procedere o meno nel percorso.

Viene richiesto Consenso informato scritto

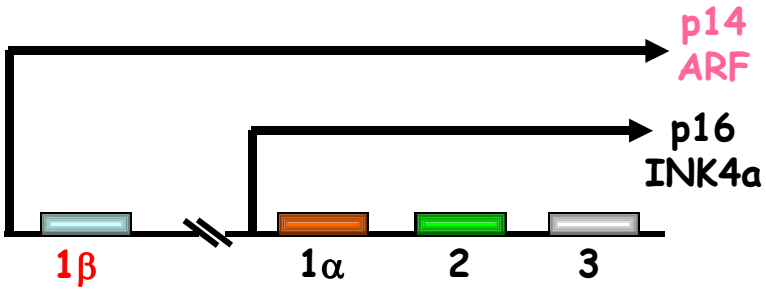
Può avvenire anche come prosecuzione immediata della prima sessione

Test diagnostico

Ove possibile, il test genetico deve essere condotto inizialmente su un familiare affetto da melanoma

Analisi dei geni candidati (*CDKN2A* e *CDK4*)
su DNA estratto da sangue periferico

Gold standard: sequenziamento diretto



Peripheral blood leukocytes

↓

DNA extraction

↓

PCR amplification of exons 1 α, 1 β, 2 e 3

↓

DIRECT SEQUENCING

Risultato del test genetico:

Mutazione identificata:

→ Test genetico predittivo nei familiari (> 18 anni)

Mutazione non identificata:

→ Test non informativo:
- Mutazione non identificabile dall'analisi attualmente disponibile
- Mutazione a carico di un gene non ancora identificato
- Coincidenza casuale

Terzo colloquio

Vengono discussi:

- Il risultato del test

- Le modalità di prevenzione e sorveglianza appropriati
(v.età prima visita dermatologica, soggetti wildtype di famiglie con mutazione identificata)

Casistica Genetica Medica, Università di Firenze:

Totale famiglie: 43

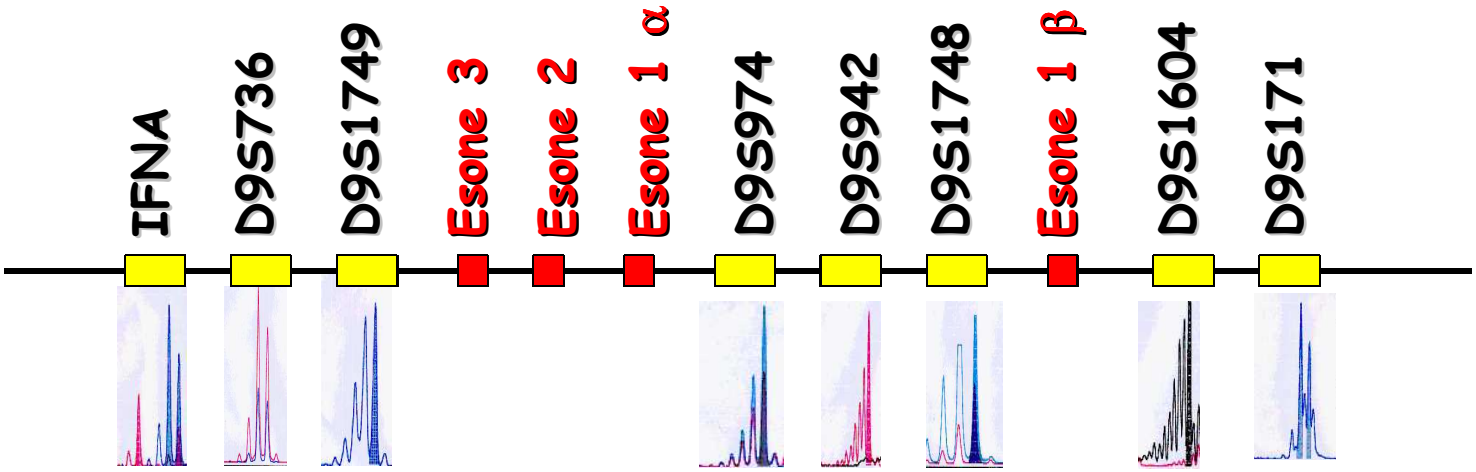
Pazienti con mutazione identificata: 11

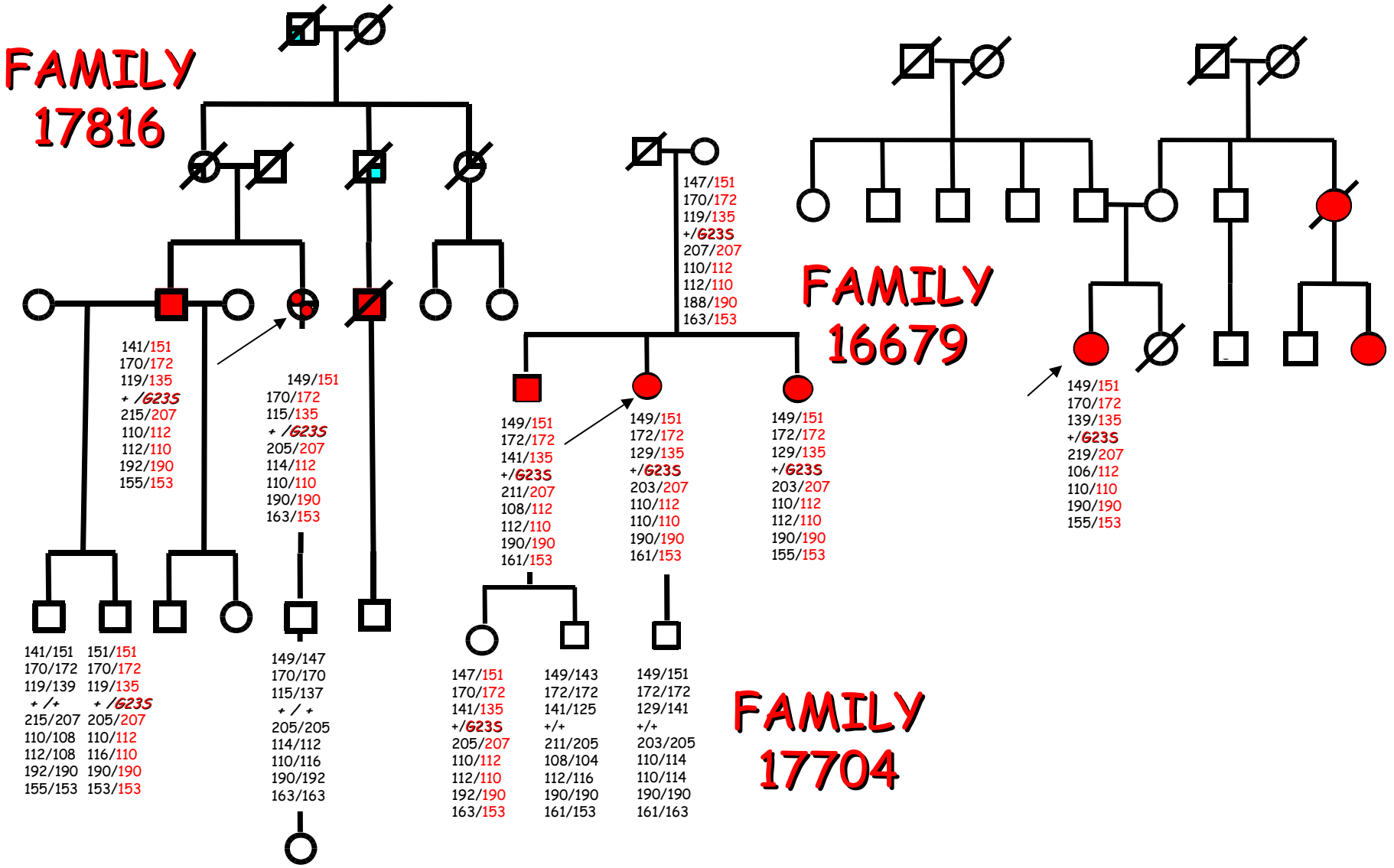
Frequenza della mutazione: 26%

Caso	Ex.1alfa	Ex.1beta	Ex.2	Ex.3
16679 °	**+/G23S**	+/+	+/+	+/+
*17704 *°*	**+/G23S**	+/+	+/+	+/+
*17816 *°*	**+/G23S**	+/+	+/+	+/+
17978 °	**+/G101W**	+/+	+/+	+/+
*18128 *°*	**+/E27→X**	+/+	+/+	+/+
*19267 **	+/+	+/+	**p16:+/L113L-P114S p14ARF:+/A128L**	+/+
20482 °	**R24P**	+/+	+/+	+/+
*21482 *°*	+/+	+/+	**p16:+/L113L-P114S p14ARF:+/A128L**	+/+
21532 °	+/+	+/+	**p16:+/L113L-P114S p14ARF:+/A128L**	+/+
*21584 **	+/+	+/+	**P16:A68L p14ARF:R82L**	+/+
*21790 **	+/+	+/+	**p16:+/L113L-P114S p14ARF:+/A128L**	+/+

°≥ 3 casi
*casi di mel.multiplo

Per verificare il possibile effetto fondatore della mutazione G23S è stato eseguito uno studio degli aplotipi mediante 8 marcatori polimorfici





L'analisi degli aplotipi nelle 3 famiglie con la mutazione G23S ha dimostrato un'origine ancestrale comune della mutazione

Melanoma Research 2007

Caso	Ex1alfa	Ex1beta	Ex.2	Ex.3
16679	**+/G23S**	+/+	+/+	+/+
17704	**+/G23S**	+/+	+/+	+/+
17816	**+/G23S**	+/+	+/+	+/+
17978	**+/G101W**	+/+	+/+	+/+
18128	**+/E27→X**	+/+	+/+	+/+
19267	+/+	+/+	**p16:+/L113L-P114S** **p14ARF:+/A128L**	+/+
20482	**R24P**	+/+	+/+	+/+
21482	+/+	+/+	**p16:+/L113L-P114S** **p14ARF:+/A128L**	+/+
21532	+/+	+/+	**p16:+/L113L-P114S** **p14ARF:+/A128L**	+/+
21584	+/+	+/+	**P16:A68L** **p14ARF:R82L**	+/+
21790	+/+	+/+	**p16:+/L113L-P114S** **p14ARF:+/A128L**	+/+

Melanomi multipli sporadici: 20 casi→ 0% mutazioni

Caso	Ex1alfa	Ex1beta	Ex2	Ex3
20188	+/+	+/+	+/+	+/+
20817	+/+	+/+	+/+	+/+
21205	+/+	+/+	+/+	+/+
21226	+/+	+/+	+/+	+/+
21286	+/+	+/+	+/+	+/+
21483	+/+	+/+	+/+	+/+
21510	+/+	+/+	+/+	+/+
21511	+/+	+/+	+/+	+/+
21535	+/+	+/+	+/+	+/+
21670	+/+	+/+	+/+	+/+
21716	+/+	+/+	+/+	+/+
21717	+/+	+/+	+/+	+/+
21718	+/+	+/+	+/+	+/+
21741	+/+	+/+	+/+	+/+
21742	+/+	+/+	+/+	+/+
21743	+/+	+/+	+/+	+/+
21773	+/+	+/+	+/+	+/+
21774	+/+	+/+	+/+	+/+
21835	+/+	+/+	+/+	+/+
22384	+/+	+/+	+/+	+/+

Mutazioni in *CDKN2A* nel 8,3-15% dei pz. con melanoma multiplo,
- nel 9-12% dei casi sporadici
- nel 47,8% di casi familiari

Puig S et al. *J Clin Oncol* 2005

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