

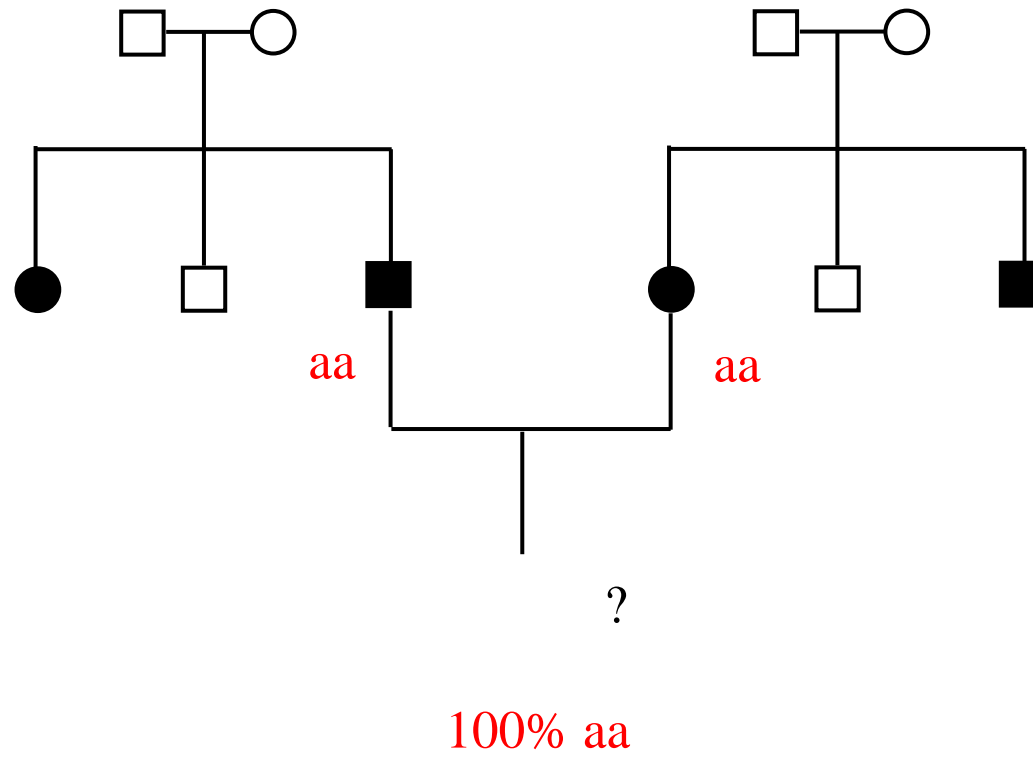
**UN GENE**



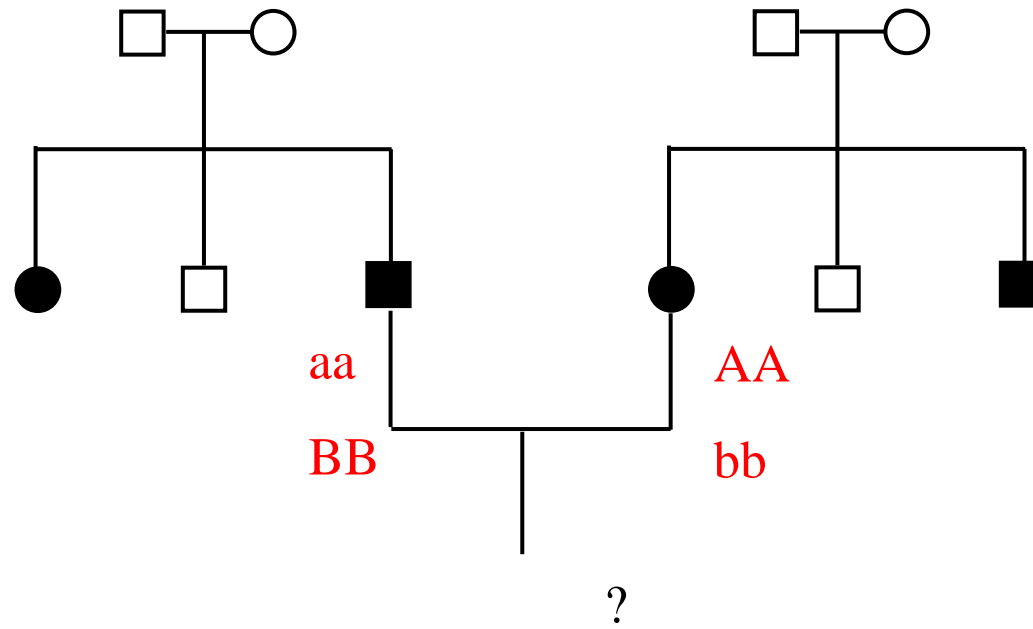
**UNA MALATTIA**

- ETEROGENEITÀ GENETICA
  - TEST DI COMPLEMENTAZIONE
    - SORDITÀ
- SERIE ALLELICHE
  - BECKER - DUCHENNE
  - INSENSITIVITÀ AGLI ANDROGENI - MALATTIA DI KENNEDY
    - AR: androgen receptor
- PENETRANZA INCOMPLETA
- ESPRESSIVITÀ VARIABILE
- INSORGENZA TARDIVA
- ANTICIPAZIONE

# Sordità



# Sordità



aa

BB

AA

bb

?

100% AaBb

# L' esempio delle sordità

**1:1000 nati presenta sordità**

In circa 50% di questi pazienti la sordità è dovuta a mutazioni in un gene

**2/3 presentano una modalità di trasmissione autosomica recessiva**

**1/3 presentano una modalità di trasmissione autosomica dominante**

**1-2% sono X-Linked**

**Esistono forme sindromiche, tuttavia la maggior parte delle sordità a trasmissione autosomica recessiva sono non sindromiche**

**Ampia eterogeneità genetica:**

**21 loci per le forme recessive**

**23 loci per le forme dominanti**

**6 loci per le forme X-Linked**

**Recenti acquisizioni:**

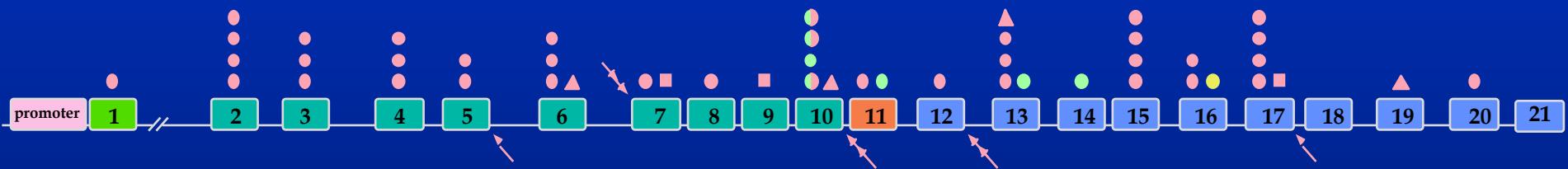
**67% delle sordità AR non sindromiche sono dovute al locus DFNB1 in 13q11-q12 nelle popolazioni dell' area mediterranea**

**La delezione di una G 35(delG) all' interno di una sequenza contenente 5 G nel gene codificante per la Connexina 26 è stata identificata nell' 80% dei pazienti con sordità al locus DFNB1**

*RET* mutations associated with HSCR (red), MEN2A-FMTC (green) and MEN2B (yellow)

● = missense or nonsense mutation    ▲ = deletion    ■ = insertion    ↗ = splice mutation

● = the same mutation associated with both MEN2A or FMTC and HSCR



## **Heterozygous missense mutations in BSCL2 are associated with distal hereditary motor neuropathy and Silver syndrome.**

**Windpassinger C, Auer-Grumbach M, Irobi J, Patel H, Petek E, Horl G, Malli R, Reed JA, Dierick I, Verpoorten N, Warner TT, Proukakis C, Van den Bergh P, Verellen C, Van Maldergem L, Merlini L, De Jonghe P, Timmerman V, Crosby AH, Wagner K.**

Institute of Medical Biology and Human Genetics, Medical University Graz, Harrachgasse 21/8, A-8010 Graz, Austria.

Distal hereditary motor neuropathy (dHMN) or distal spinal muscular atrophy (OMIM #182960) is a heterogeneous group of disorders characterized by an almost exclusive degeneration of motor nerve fibers, predominantly in the distal part of the limbs. Silver syndrome (OMIM #270685) is a rare form of hereditary spastic paraparesis mapped to chromosome 11q12-q14 (SPG17) in which spasticity of the legs is accompanied by amyotrophy of the hands and occasionally also the lower limbs. Silver syndrome and most forms of dHMN are autosomal dominantly inherited with incomplete penetrance and a broad variability in clinical expression. A genome-wide scan in an Austrian family with dHMN-V (ref. 4) showed linkage to the locus SPG17, which was confirmed in 16 additional families with a phenotype characteristic of dHMN or Silver syndrome. After refining the critical region to 1 Mb, we sequenced the gene Berardinelli-Seip congenital lipodystrophy (BSCL2) and identified two heterozygous missense mutations resulting in the amino acid substitutions N88S and S90L. Null mutations in BSCL2, which encodes the protein seipin, were previously shown to be associated with autosomal recessive Berardinelli-Seip congenital lipodystrophy (OMIM #269700). We show that seipin is an integral membrane protein of the endoplasmic reticulum (ER). The amino acid substitutions N88S and S90L affect glycosylation of seipin and result in aggregate formation leading to neurodegeneration.

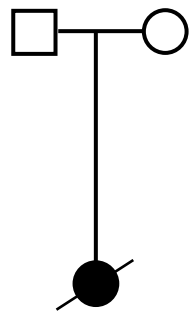
# Oloprosencefalia

**Il più frequente difetto di sviluppo della linea mediana**

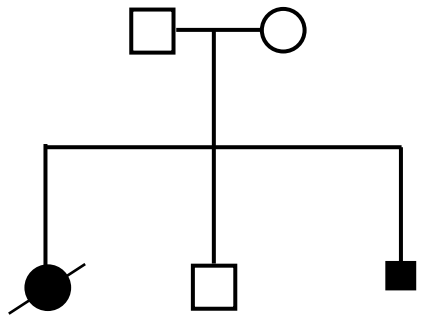
**Frequenza: 1:16000 nati**

**Geneticamente e fenotipicamente eterogeneo**

**Espressione clinica è variabile, con i casi estremi che presentano anoftalmia o ciclopia**







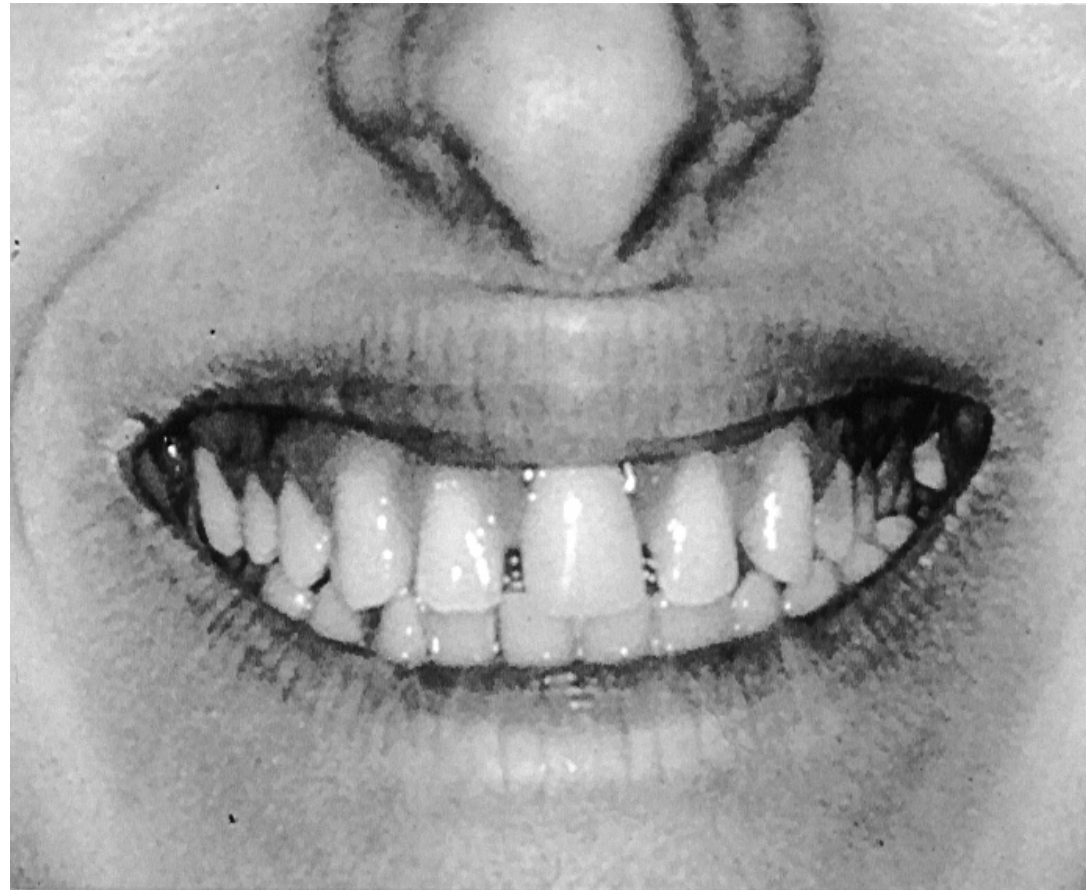
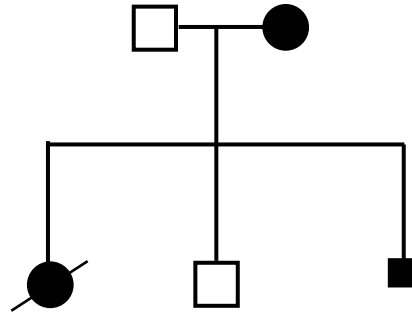


Fig. 2a

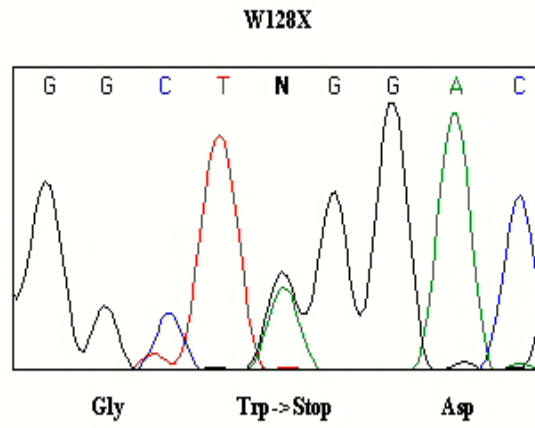
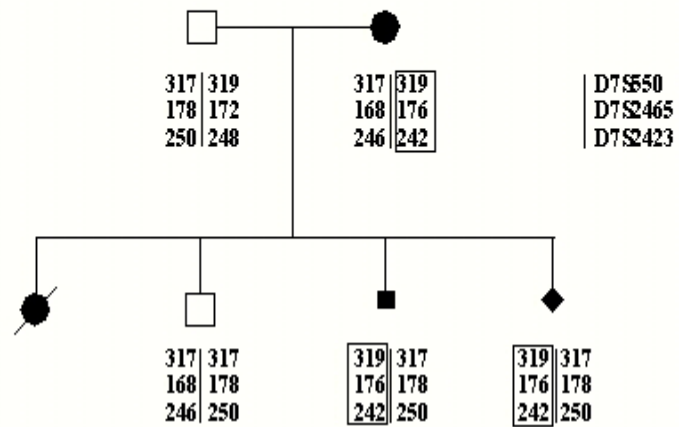


Fig. 2b

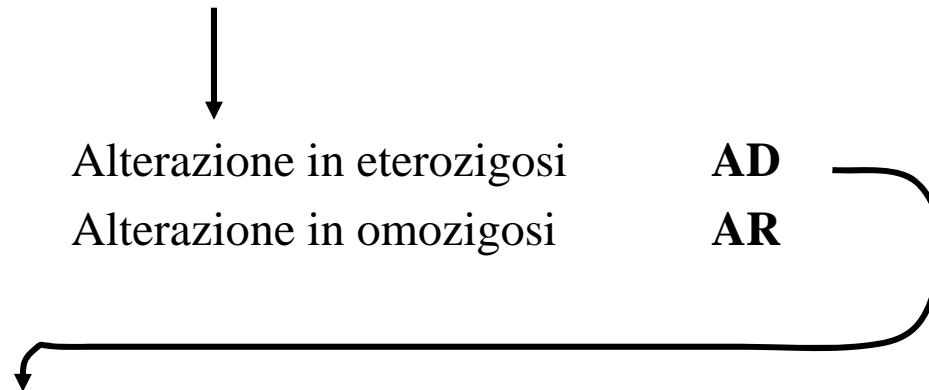


## PENETRANZA INCOMPLETA

- Penetranza incompleta è una frequente complicazione di un carattere dominante.
- La penetranza di un carattere, per un determinato fenotipo, è definita come la probabilità che una persona che presenta l'alterazione a livello genotipico manifesterà il carattere.
- Un carattere con penetranza completa (100%) deve manifestarsi in tutte le persone eterozigoti per quel carattere.
- Un indice di penetranza incompleta è il salto di generazione per certi caratteri quando si costruisce un albero genealogico.
- È facile spiegare la penetranza incompleta se pensiamo ad un “locus genetico” non isolato ma in un contesto differente da persona a persona (background genetico), sotto l'influenza di geni che possono modificare il fenotipo (GENI MODIFICATORI).

# ESPRESSIVITÀ VARIABILE

- Correlata con la penetranza incompleta c'è l'“espressività variabile”, che è presente soprattutto in condizioni dominanti.
- Differenti membri della stessa famiglia mostrano spettri fenotipici differenti della stessa malattia.
- Le cause sono comuni a quelle responsabili della penetranza incompleta: l'influenza di altri geni o di fattori ambientali possono influire sullo sviluppo dei sintomi di una malattia.
- Penetranza Incompleta ed Espressività Variabile possono occasionalmente essere osservate in difetti genetici ad ereditarietà recessiva



È più variabile perché coinvolge il bilanciamento dell'effetto di due alleli.

## Geni responsabili di Oloprosencefalia

SHH (Sonic hedgehog)

3,7% casi sporadici

18 % casi familiari

ZIC2

5% casi sporadici e familiari

SIX3

1% casi sporadici e familiari

TGIF

1% casi sporadici e familiari

PATCHED1

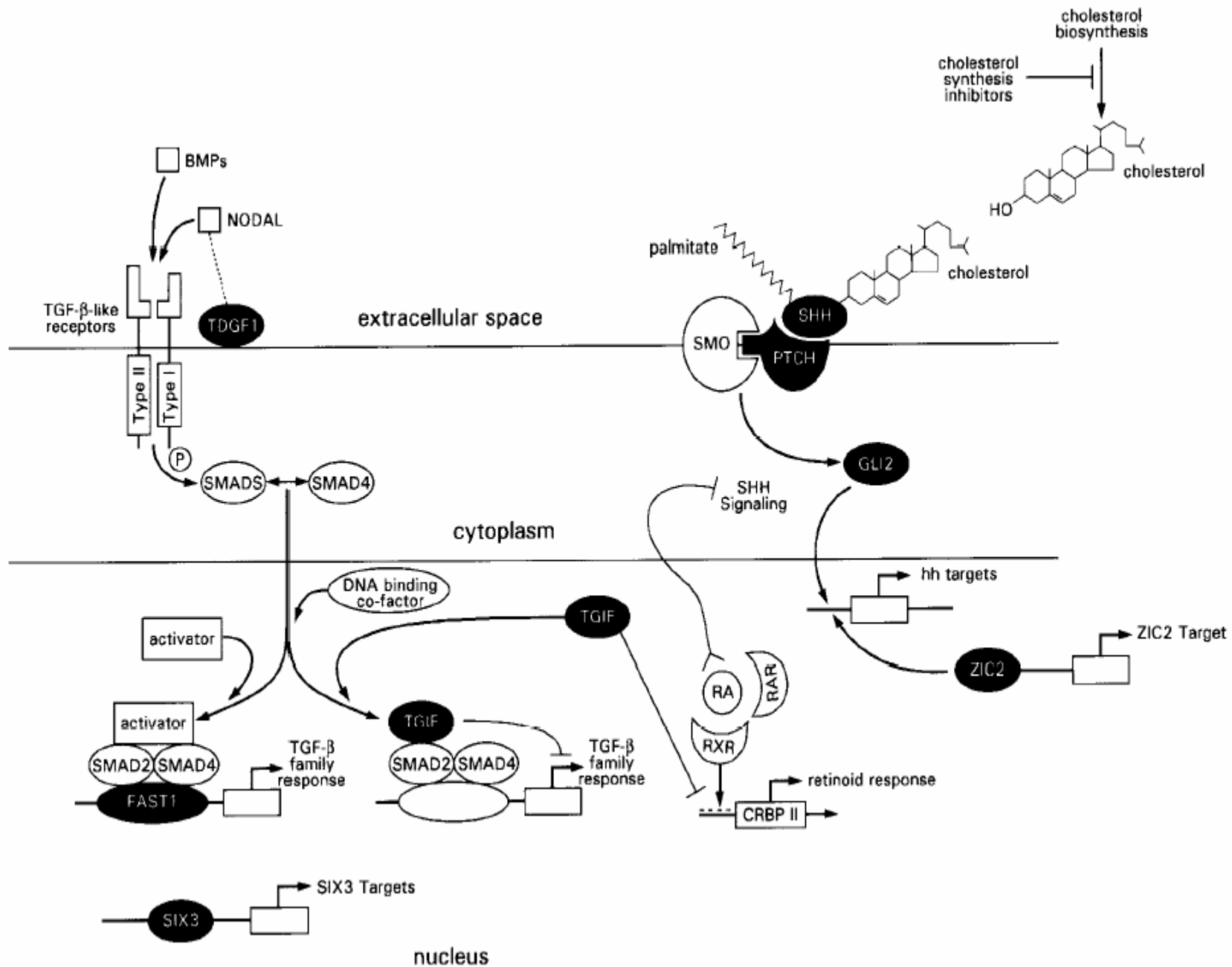
SHH signaling

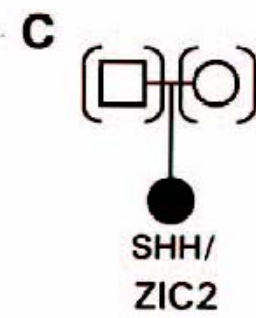
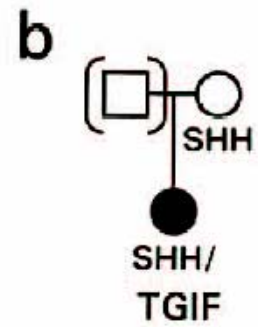
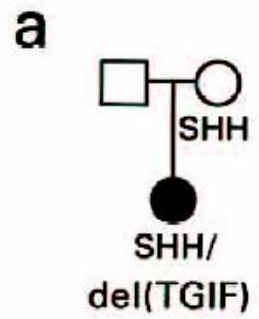
GLI2

TDGF1

Nodal /TGF- $\beta$  pathway

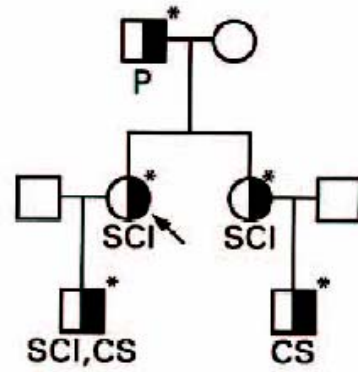
FAST1







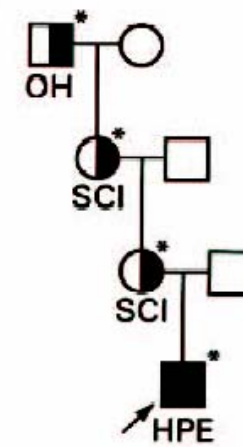
d



\* SHH Mutation



e



**Table 1**

**Digenic Inheritance in Human Disease**

EFFECT AND PHENOTYPE	GENE 1		GENE 2		REFERENCE
	Mutation	Phenotype	Mutation	Phenotype	
<b>Synergistic:</b>					
RP	<i>ROM1</i> <sup>+/G80insG</sup>	Normal	<i>RDS</i> <sup>+/L185P</sup>	Normal	Kajiwara et al. 1994
RP	<i>ROM1</i> <sup>+/L114insG</sup>	Normal	<i>RDS</i> <sup>+/L185P</sup>	Normal	Kajiwara et al. 1994
Bardet-Biedl	<i>BBS2</i> <sup>Y24X/Q59X</sup>	Normal	<i>BBS6</i> <sup>+/Q147X</sup>	Normal	Katsanis et al. 2001
Deafness	<i>GJB2</i> <sup>+/35delG</sup>	Normal	<i>GJB6</i> <sup>+/-</sup>	Normal	Lerer et al. 2001
Deafness	<i>GJB2</i> <sup>+/167delT</sup>	Normal	<i>GJB6</i> <sup>+/-</sup>	Normal	del Castillo et al. 2002
Hirschsprung	<i>RET</i> <sup>+/164711</sup>	Normal	<i>EDNRB</i> <sup>+/S305N</sup>	Normal	Auricchio et al. 1999
Severe insulin resistance	<i>PPARG</i> <sup>+/A.553delAAAiT</sup>	Normal	<i>PPP1R3A</i> <sup>+/C.1984delAG</sup>	Normal	Savage et al. 2002
<b>Modifier:</b>					
Juvenile-onset glaucoma	<i>MYOC</i> <sup>+/G399V</sup>	Adult-onset glaucoma	<i>CYP11B1</i> <sup>+/R.368H</sup>	Normal	Vincent et al. 2002
Usher 1	<i>USH3</i> <sup>mut/mut</sup>	Usher 3	<i>MYO7A</i> <sup>+/delG (exon 25)</sup>	Normal	Adato et al. 1999
Congenital nonlethal JEB	<i>COL17A1</i> <sup>R1226X/L855X</sup>	Juvenile JEB	<i>LAMB3</i> <sup>+/R635X</sup>	Normal	Floeth et al. 1999
More severe ADPKD	<i>PKD1</i> <sup>+/mut</sup>	Less severe ADPKD	<i>PKD2</i> <sup>+/2152delA</sup>	Less severe ADPKD	Pei et al. 2001
More severe hearing loss	<i>DFNA1</i>	Mild hearing loss	<i>DFNA2</i>	Mild hearing loss	Balciuniene et al. 1998
WS2/OA	<i>MITF</i> <sup>+/944delA</sup>	?WS2	<i>TYR</i> <sup>+/R402Q</sup>	Normal	Morell et al. 1997
More severe WS2/OA	<i>MITF</i> <sup>+/944delA</sup>	?WS2	<i>TYR</i> <sup>R402Q/R402Q</sup>	Normal	

NOTE.—The phenotypic description applies to the family reported in the reference only. mut = haplotype consistent with mutation in the gene; + = wild type; - = partial deletion of gene.

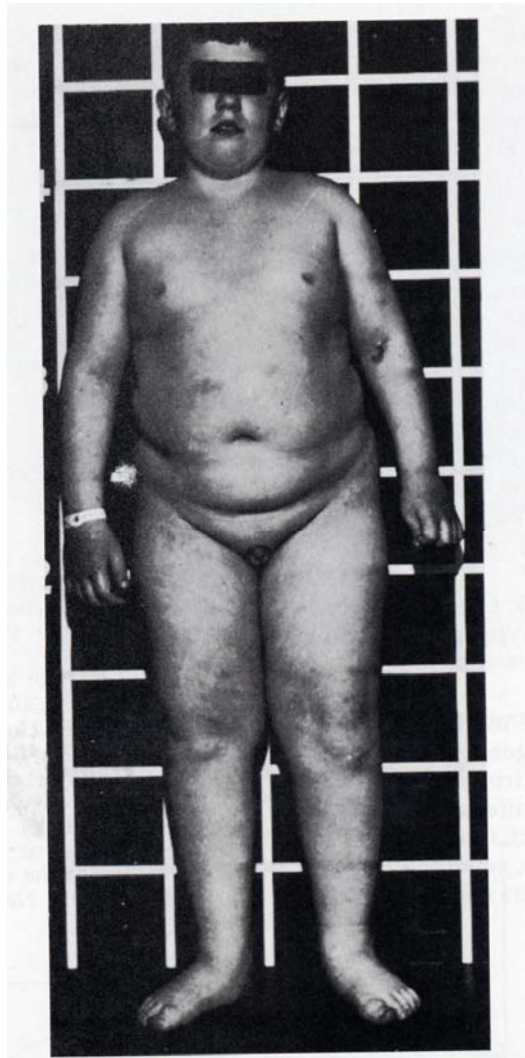


FIGURE 1. Bardet-Biedl syndrome. A 10-year-old male with retinal pigmentation and renal insufficiency. Obesity from birth. I.Q. of 52.

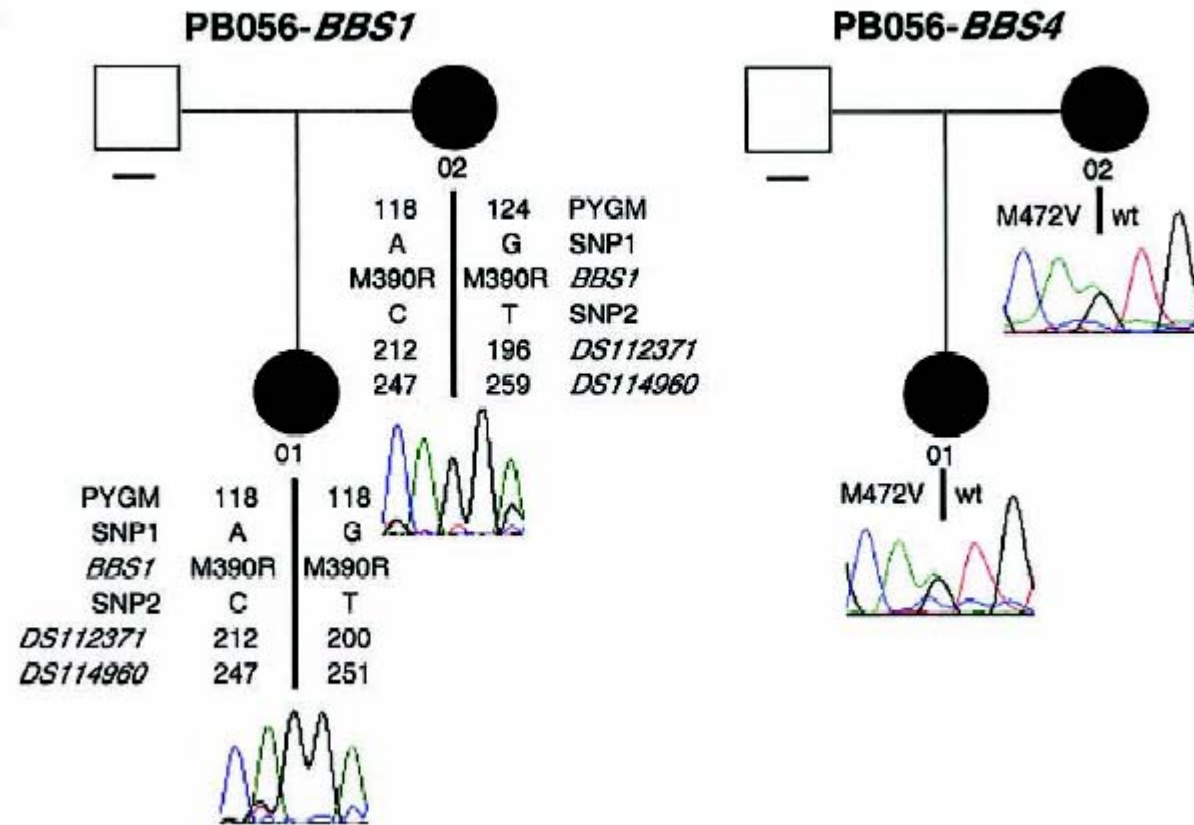
## Genetic Interaction of *BBS1* Mutations with Alleles at Other *BBS* Loci Can Result in Non-Mendelian Bardet-Biedl Syndrome

Philip L. Beales,<sup>1,\*</sup> Jose L. Badano,<sup>3,\*</sup> Alison J. Ross,<sup>1</sup> Stephen J. Ansley,<sup>3</sup> Bethan E. Hoskins,<sup>1</sup> Brigitta Kirsten,<sup>2</sup> Charles A. Mein,<sup>2</sup> Philippe Froguel,<sup>2,5</sup> Peter J. Scambler,<sup>1</sup> Richard Alan Lewis,<sup>6,7,8,9</sup> James R. Lupski,<sup>6,8</sup> and Nicholas Katsanis<sup>3,4</sup>

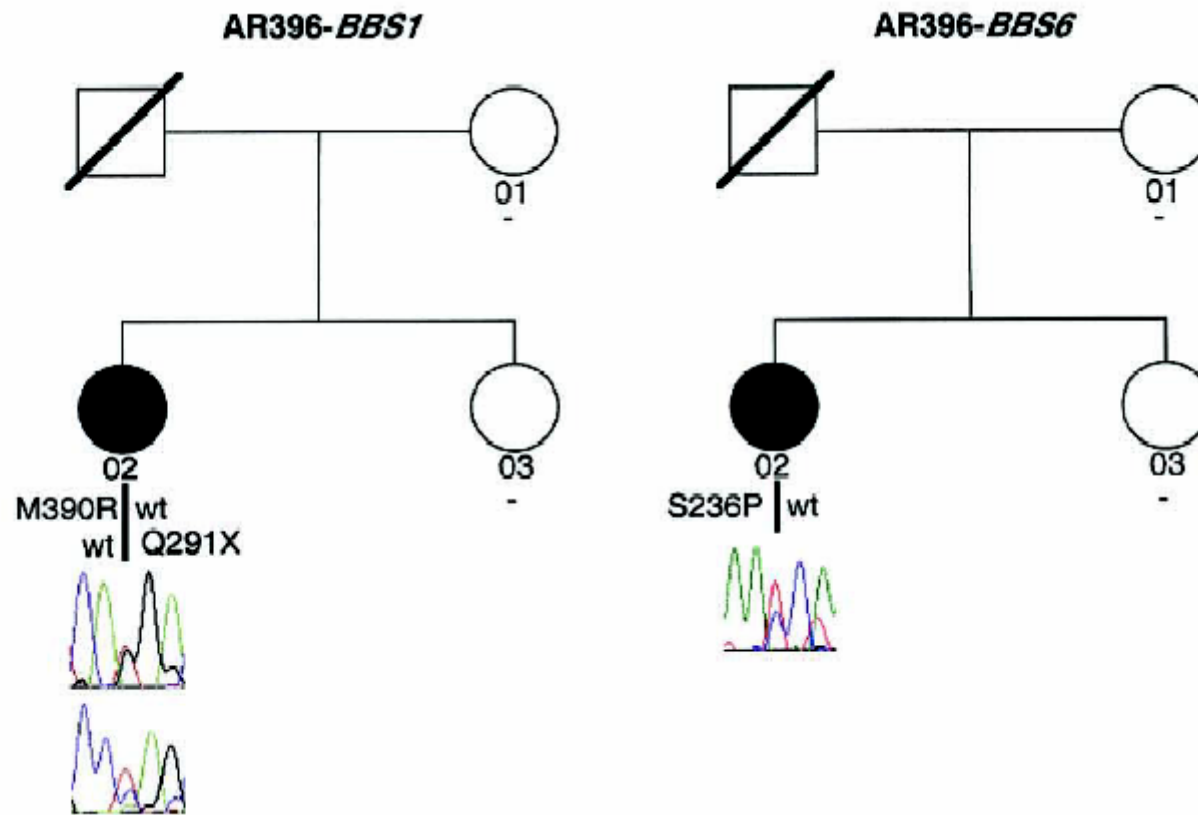
<sup>1</sup>Molecular Medicine Unit, Institute of Child Health, University College London, <sup>2</sup>Genome Centre, Barts and the London, Queen Mary's School of Medicine and Dentistry, London; <sup>3</sup>Institute of Genetic Medicine and <sup>4</sup>Wilmer Eye Institute, Johns Hopkins University, Baltimore; <sup>5</sup>CNR-Institute of Biology, Pasteur Institute, Lille, France; and Departments of <sup>6</sup>Molecular and Human Genetics, <sup>7</sup>Ophthalmology, <sup>8</sup>Pediatrics, and <sup>9</sup>Medicine, Baylor College of Medicine, Houston

Bardet-Biedl syndrome is a genetically and clinically heterogeneous disorder caused by mutations in at least seven loci (*BBS1–7*), five of which are cloned (*BBS1*, *BBS2*, *BBS4*, *BBS6*, and *BBS7*). Genetic and mutational analyses have indicated that, in some families, a combination of three mutant alleles at two loci (triallelic inheritance) is necessary for pathogenesis. To date, four of the five known *BBS* loci have been implicated in this mode of oligogenic disease transmission. We present a comprehensive analysis of the spectrum, distribution, and involvement in non-Mendelian trait transmission of mutant alleles in *BBS1*, the most common *BBS* locus. Analyses of 259 independent families segregating a *BBS* phenotype indicate that *BBS1* participates in complex inheritance and that, in different families, mutations in *BBS1* can interact genetically with mutations at each of the other known *BBS* genes, as well as at unknown loci, to cause the phenotype. Consistent with this model, we identified homozygous M390R alleles, the most frequent *BBS1* mutation, in asymptomatic individuals in two families. Moreover, our statistical analyses indicate that the prevalence of the M390R allele in the general population is consistent with an oligogenic rather than a recessive model of disease transmission. The distribution of *BBS* oligogenic alleles also indicates that all *BBS* loci might interact genetically with each other, but some genes, especially *BBS2* and *BBS6*, are more likely to participate in triallelic inheritance, suggesting a variable ability of the *BBS* proteins to interact genetically with each other.

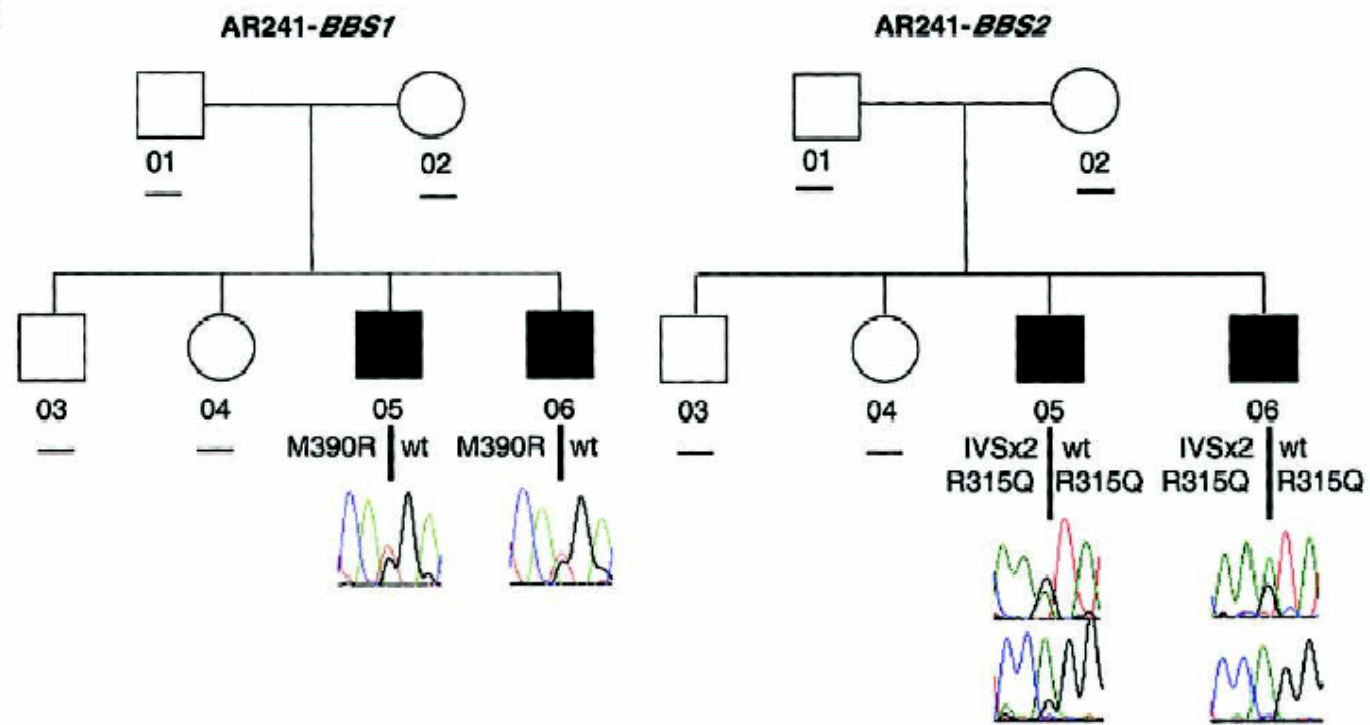
A

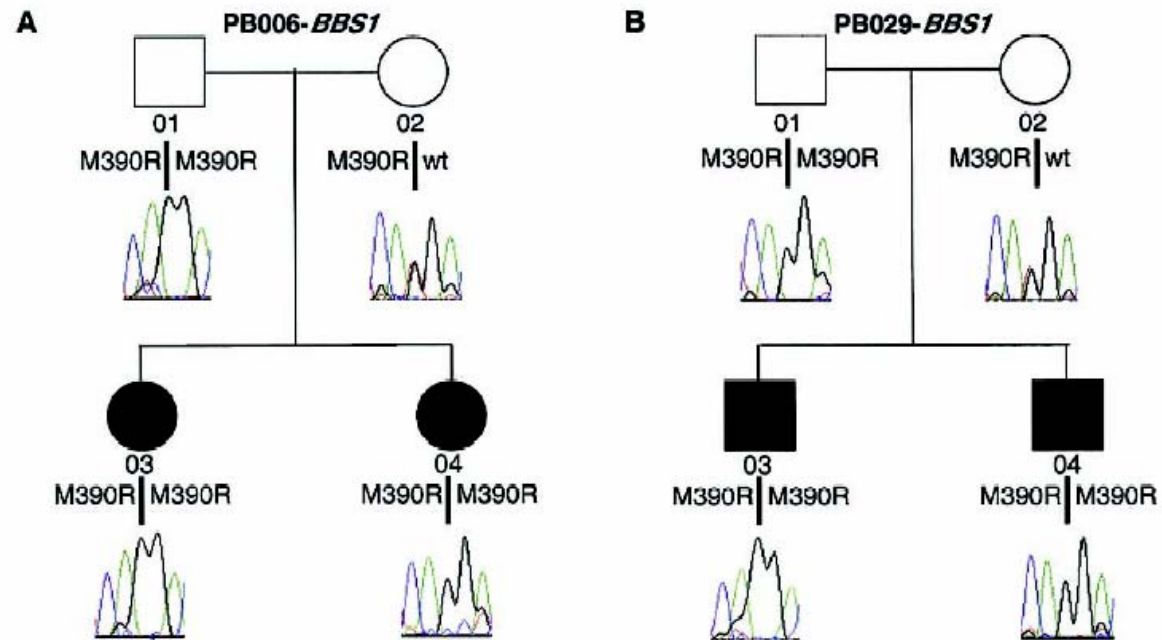


**B**



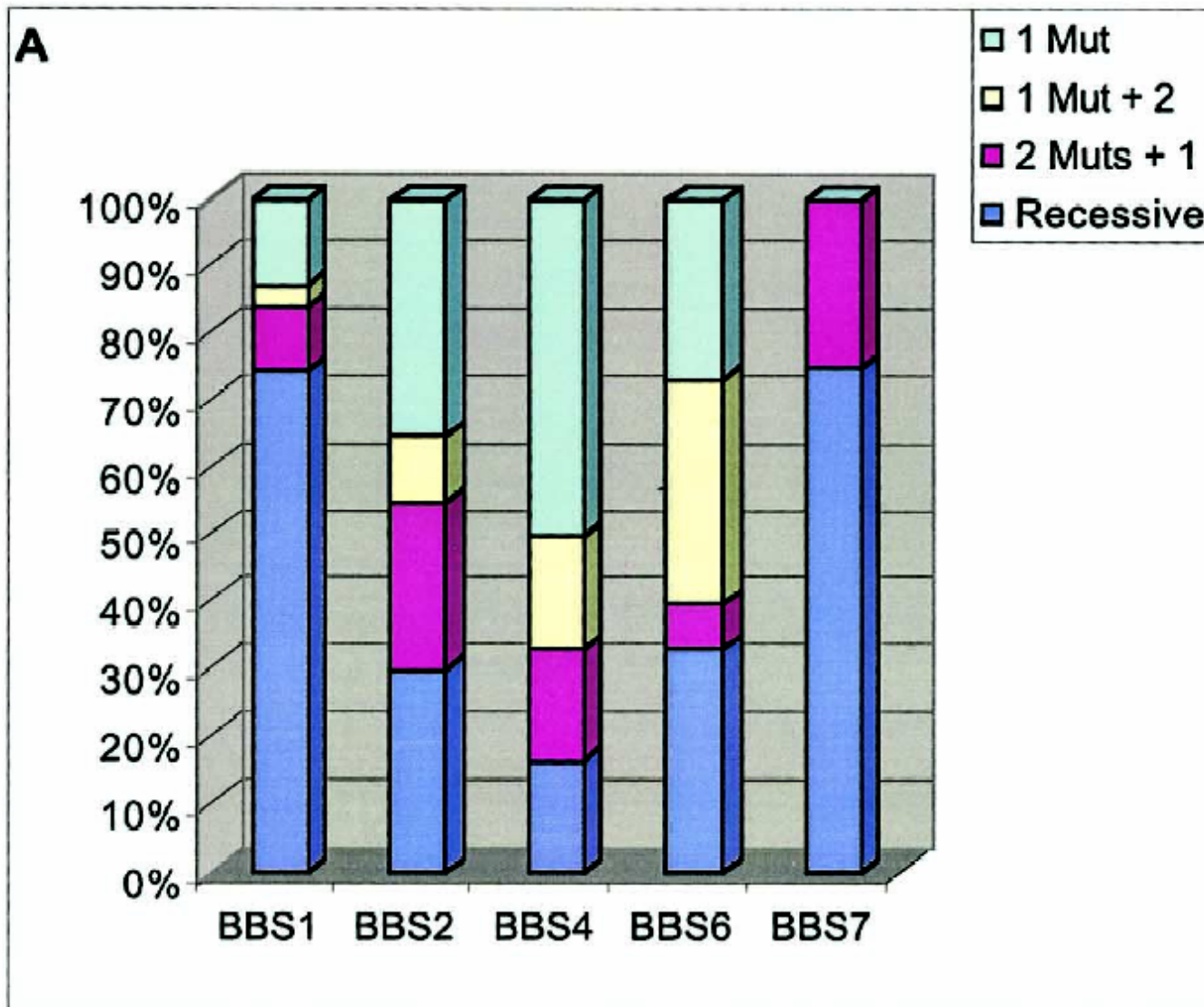
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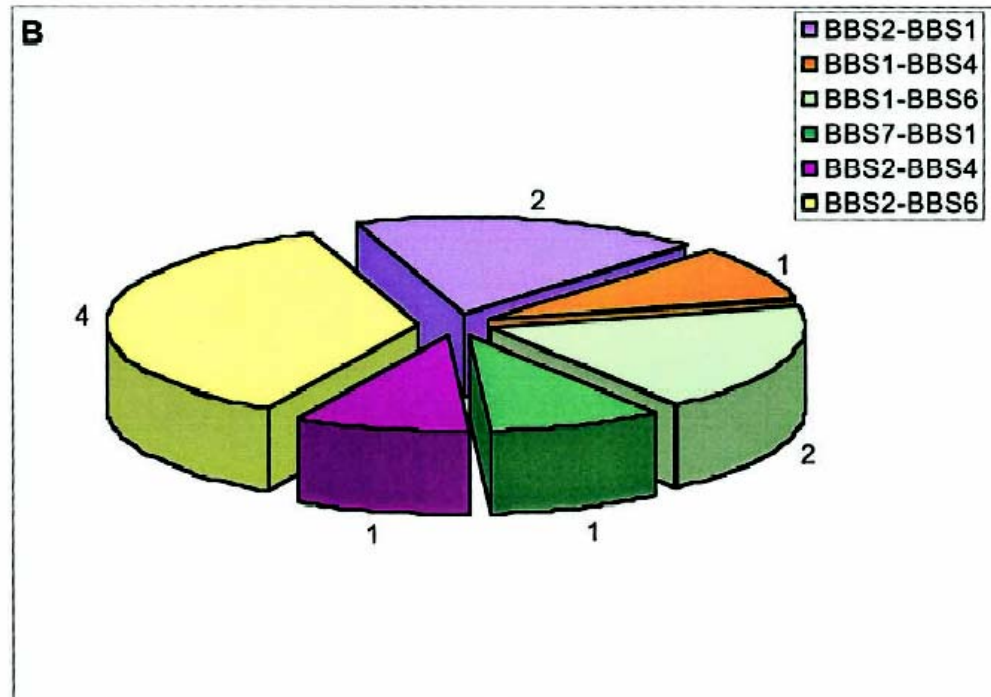




**Figure 3** Two M390R mutations are not sufficient for pathogenesis. In pedigrees PB006 (A) and PB029 (B), the unaffected father is homozygous for the common M390R allele, as are all affected individuals. A third mutation has not yet been found in these two families.







**Figure 4** Analysis of triallelism. *A*, Bar graph demonstrating the distribution of recessive and complex alleles in each of the five cloned *BBS* genes. The relative contribution of one or two alleles is also indicated. *B*, Pie chart depicting the prevalence of locus combinations in families with complex BBS. Combinations were scored irrespective of the number of alleles provided by each locus. Numbers outside each slice indicate how many families exhibit each locus combination.

## Heterozygous mutations in *BBS1*, *BBS2* and *BBS6* have a potential epistatic effect on Bardet–Biedl patients with two mutations at a second BBS locus

Jose L. Badano<sup>1</sup>, Jun Chul Kim<sup>2</sup>, Bethan E. Hoskins<sup>3</sup>, Richard Alan Lewis<sup>4</sup>,  
Stephen J. Ansley<sup>1</sup>, David J. Cutler<sup>1</sup>, Claudio Castellan<sup>5</sup>, Philip L. Beales<sup>3</sup>,  
Michel R. Leroux<sup>2</sup> and Nicholas Katsanis<sup>1,5,6,\*</sup>

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<sup>2</sup>Department of Molecular Biology and Biochemistry, Simon Fraser University, Burnaby, BC, Canada V5A 1S6,

<sup>3</sup>Molecular Medicine Unit, Institute of Child Health, University College London, London WC1N 1EH, UK, <sup>4</sup>Departments of Molecular and Human Genetics, Ophthalmology, Pediatrics, and Medicine, Baylor College of Medicine, One Baylor Plaza, Houston TX 77030, USA, <sup>5</sup>The Clinical Genetics Service, Bolzano General Hospital, Bolzano 39100, Italy and

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Received March 3, 2003; Revised and Accepted May 19, 2003

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**Bardet–Biedl syndrome (BBS) is a pleiotropic genetic disorder with substantial inter- and intrafamilial variability, that also exhibits remarkable genetic heterogeneity, with seven mapped BBS loci in the human genome. Recent data have demonstrated that BBS may be inherited either as a simple Mendelian recessive or as an oligogenic trait, since mutations at two loci are sometimes required for pathogenesis. This observation suggests that genetic interactions between the different BBS loci may modulate the phenotype, thus contributing to the clinical variability of BBS. We present three families with two mutations in either *BBS1* or *BBS2*, in which some but not all patients carry a third mutation in *BBS1*, *BBS2* or the putative chaperonin *BBS6*. In each example, the presence of three mutant alleles correlates with a more severe phenotype. For one of the missense alleles, we also demonstrate that the introduction of the mutation in mammalian cells causes a dramatic mislocalization of the protein compared with the wild-type. These data suggest that triallelic mutations are not always necessary for disease manifestation, but might potentiate a phenotype that is caused by two recessive mutations at an independent locus, thus introducing an additional layer of complexity on the genetic modeling of oligogenicity.**

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## Sindrome di Van der Woude

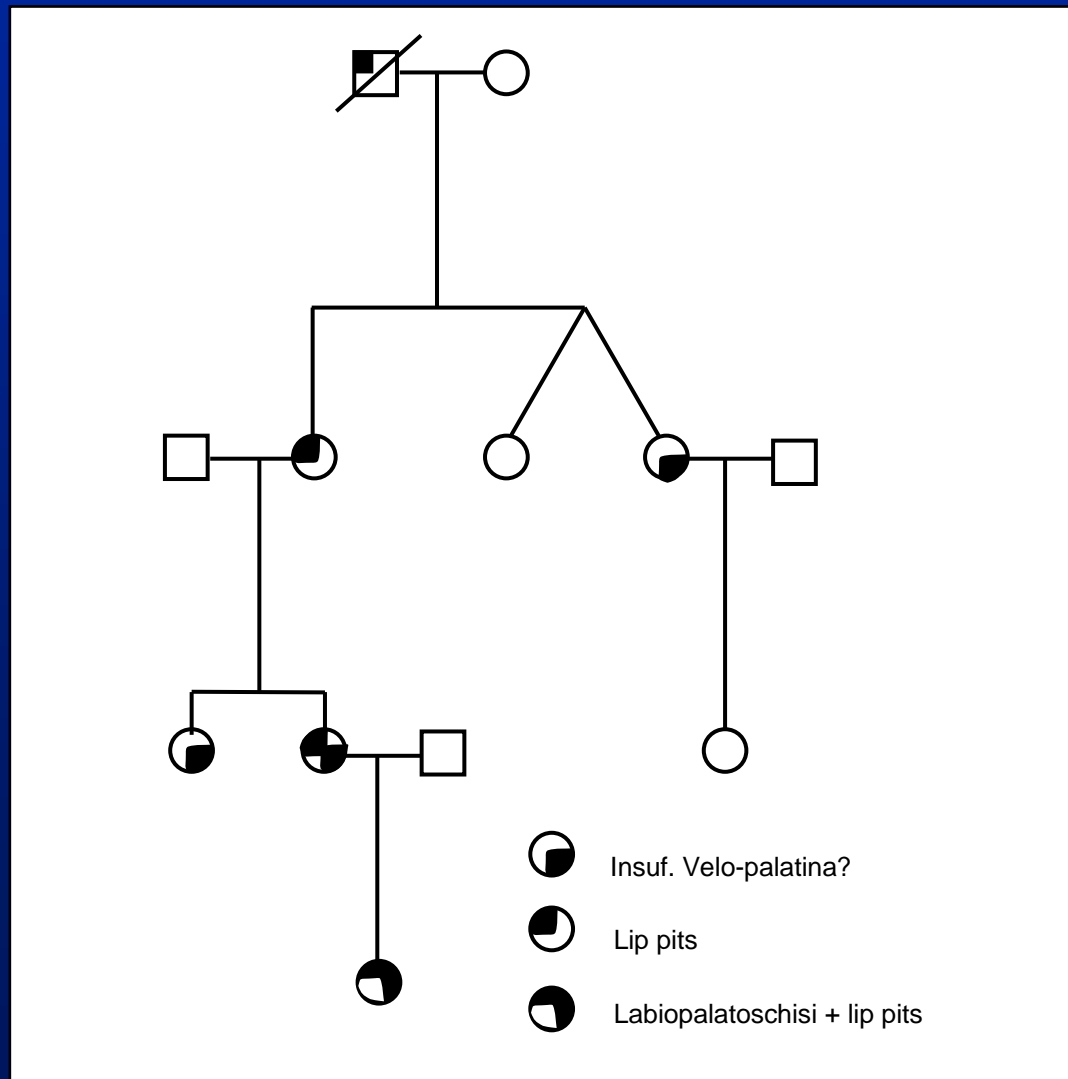
- Anomalia sviluppo multisistemica a prevalente coinvolgimento cranio-facciale
- Labbro inferiore: *lip pit, lip mound, lip sinus*  
persistenza di ghiandole salivari accessorie
- Ipoplasia mascellare, ipodontia,  
labio-palatoschisi e palatoschisi
- La piu' frequente sindrome associata a  
labio-palatoschisi

## Sindrome di Van der Woude: Genetica

- Carattere autosomico dominante ad espressività variabile e penetranza incompleta
- Eterogeneità genetica di locus
  - 1) Linkage 1q32-q41 : gene IRF6  
Sindrome Pterigio Popliteo Allelica
  - 2) Linkage 1p34
- Proposto Gene modificatore in 17p11.2-p11.1

# Sindrome di Van der Woude: caso familiare

15 individui, 4 generazioni, 6 individui affetti?



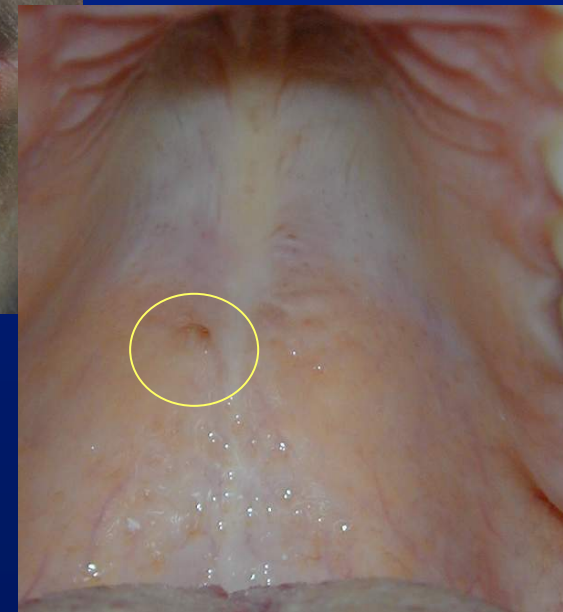
# Sindrome di Van der Woude: caso familiare

15 individui, 4 generazioni, 6 individui affetti ?

La probanda: CLP e  
anomalia labiale



La madre: lip sinuses,  
anomalia palato duro



## Sindrome di Van der Woude: caso familiare

La zia: otiti ricorrenti, voce nasale,  
sospetta insuf. velo-palatina



La nonna: lip pits

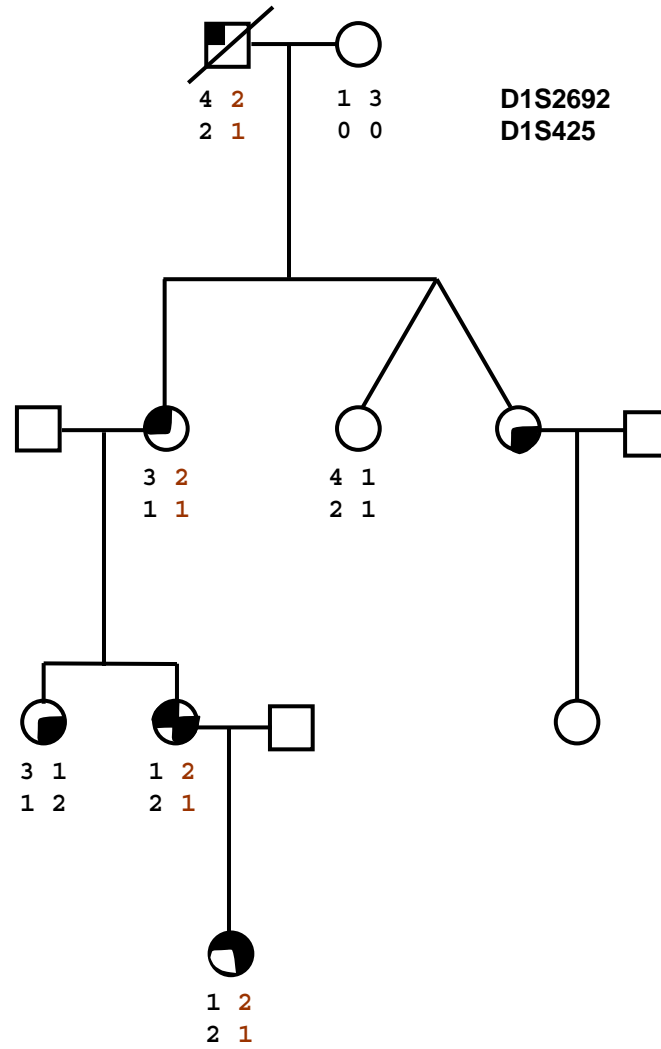


Il bis-nonno: lip sinuses








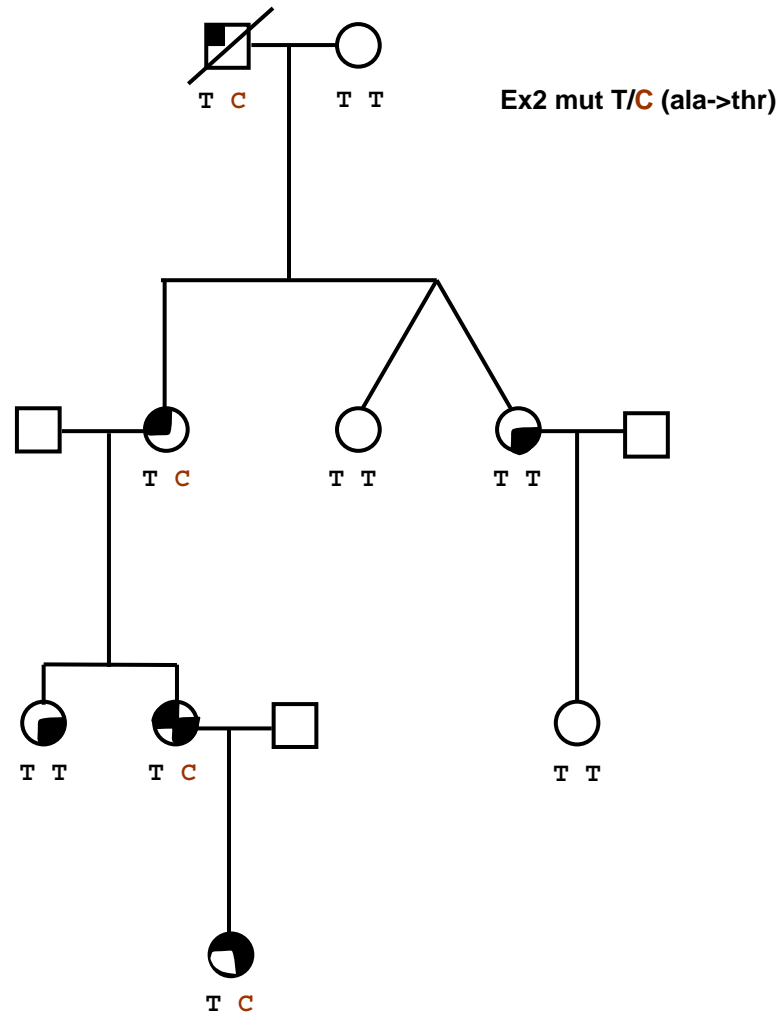
Van der Woude Syndrome






D1S2692  
D1S425

-  Insuf. Velo-palatina?
-  Lip pits
-  Labiopalatoschisi + lip pits

# Van der Woude Syndrome



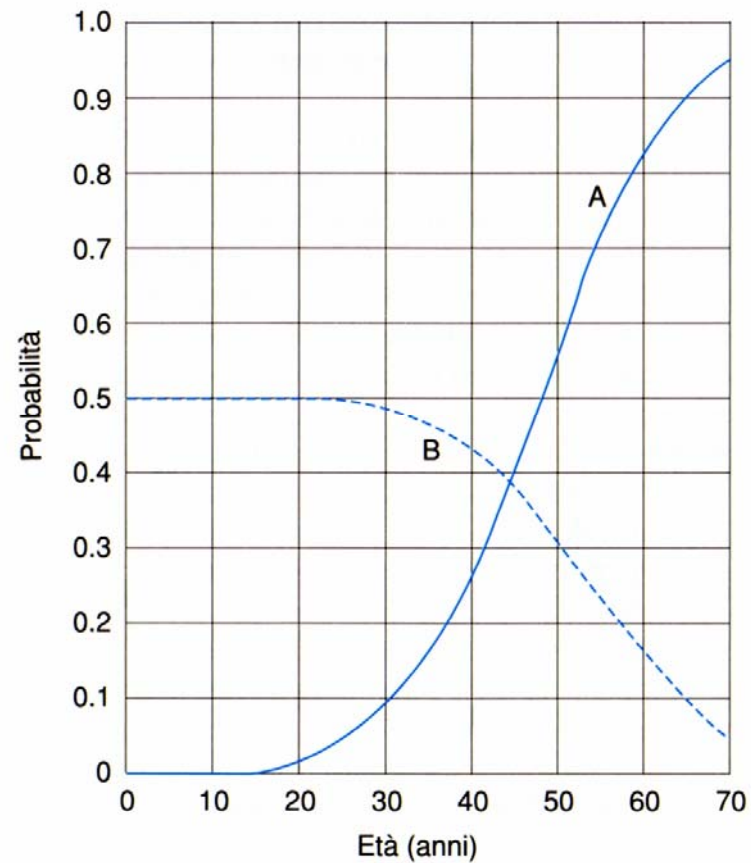
-  Insuf. Velo-palatina?
-  Lip pits
-  Labiopalatoschisi + lip pits

## Considerazioni

- Ridotta penetranza complica la consulenza
- Estrema variabilità di espressione:
  - anomalie labiali minori
  - anomalie minori del palato duro
- Consulenza genetica e inquadramento CLP
- Analisi mutazionale IRF6

# MALATTIE AD INSORGENZA TARDIVA

- Un caso particolarmente importante di penetranza ridotta è rappresentato dalle “malattie ad insorgenza tardiva”.
- Le malattie genetiche non necessariamente devono essere “congenite”.
- Quelle congenite sono quelle che si presentano alla nascita.
- In alcune malattie, sebbene l’alterazione genetica sia presente fin dalla nascita, il quadro clinico può manifestarsi nell’età adulta.
- Il ritardo nell’insorgenza può essere dovuto a:
  - lento accumulo di sostanze nocive
  - morte rallentata di certi tessuti
  - incapacità di riparare certe forme di danno ambientale
  - geni oncosoppressori
  - cause sconosciute

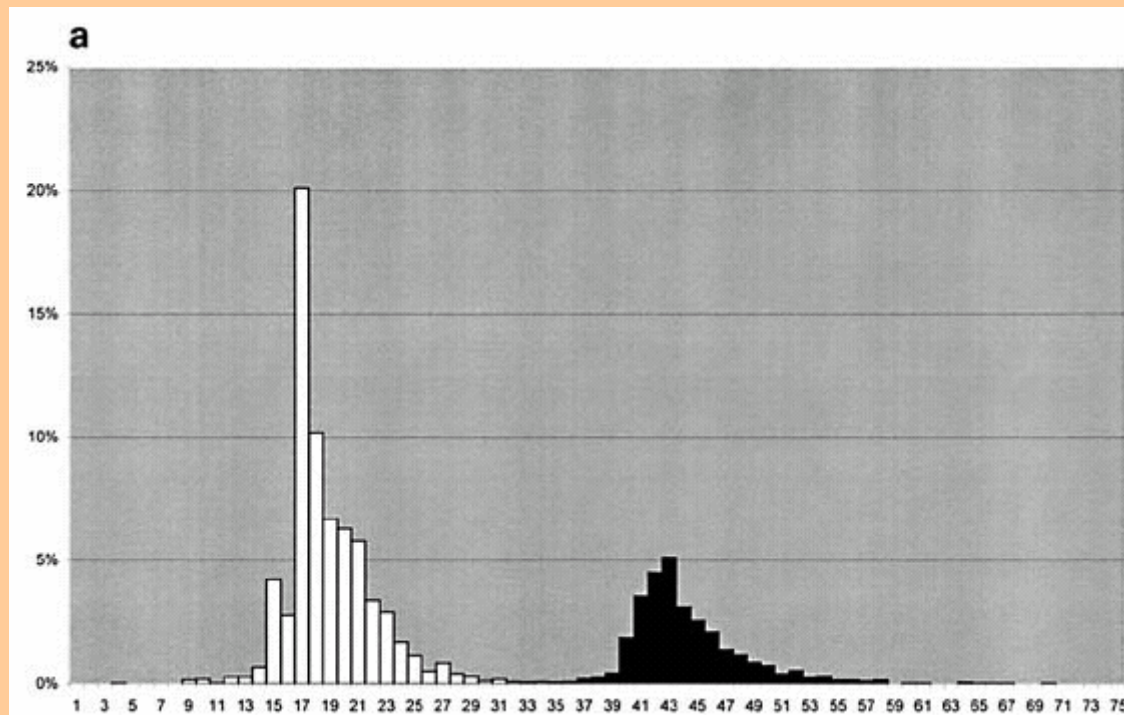
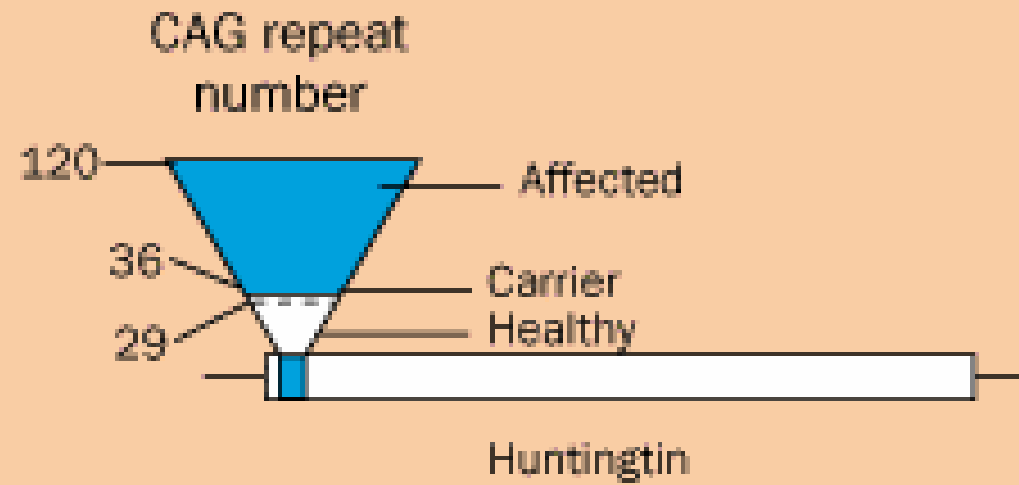
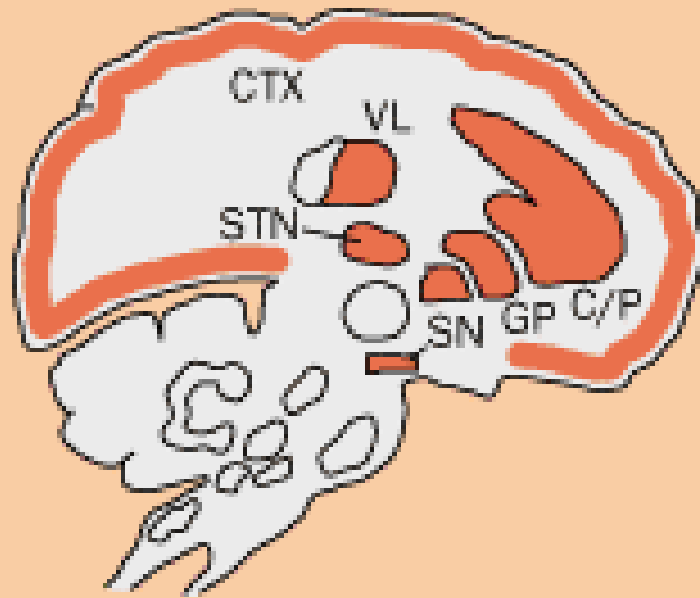


**A** probabilità di un individuo che ha il gene malattia di sviluppare i sintomi ad una certa età.



**B** rischio di un individuo figlio di un affetto di portare il gene malattia ad una determinata età.

# ANTICIPAZIONE

- L'anticipazione è un caso particolare di “espressività variabile”.
- L'anticipazione descrive la tendenza da parte di alcune malattie genetiche a trasmissione autosomica dominante di divenire più gravi nelle generazioni successive.
- L'anticipazione può essere mascherata da variazioni casuali della severità.
- In molti casi può essere riferita ad errori della diagnosi.
- Il fenomeno dell'anticipazione è stato spiegato con l'instabilità di certi trinucleotidi repeat che possono espandersi in certe malattie (X - Fragile, Distrofia Miotonica, Malattia di Huntington).
- La severità e l'età di insorgenza in queste malattie correla con la lunghezza del repeat e questa tende ad espandersi attraverso le generazioni.



# LA HUNTINGTINA

- ⌘ Il gene codifica per una proteina di 330 kD: la Huntingtina
- ⌘ Sequenza trinucleotidica CAG ripetuta nella porzione codificante del gene
- ⌘ Numero ripetizioni:
  -  soggetti normali: 9-32
  -  soggetti con HD: 37-80



# Correlazione n° ripetizioni CAG / età esordio

🎗 *Esordio giovanile: 60-80 triplette*

🎗 *Esordio tardivo: 40-50 triplette*