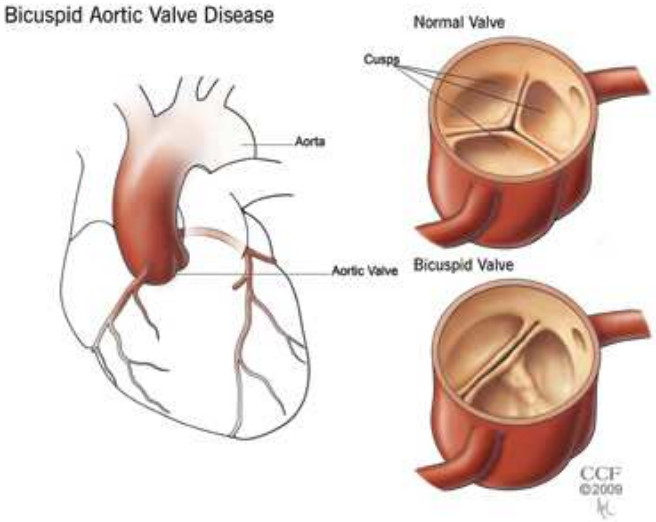
NOTCH1 gene mutations in patients with familial Bicuspid Aortic Valve

Paola Panesi, Ilenia Foffa, Lamia Ait Ali, Cecilia Vecoli, Pierluigi Festa, Maria Grazia Andreassi

Istituto di Fisiologia Clinica, CNR

Padova 16-19 ottobre 2013

Bicuspid Aortic Valve



It's a defect of the aortic valve that results in the formation of two leaflets or cusps instead of the normal three.

- **Most common cardiovascular malformation in human: prevalence 1-2%.**
- **Male predominance (≈ 2:1 ratio).**
- **Association with other CVMs :**

  - Coarctation of the aorta (50% to 80%)
  - Interruption of the aorta (36%)
  - Isolated ventricular septal defect (20%)
  - Infrequently other CVMs

Journal of the American College of Cardiology
© 2004 by the American College of Cardiology Foundation
Published by Elsevier Inc.

Vol. 44, No. 1, 2004
ISSN 0735-1097/04/$30.00
doi:10.1016/j.jacc.2004.03.050

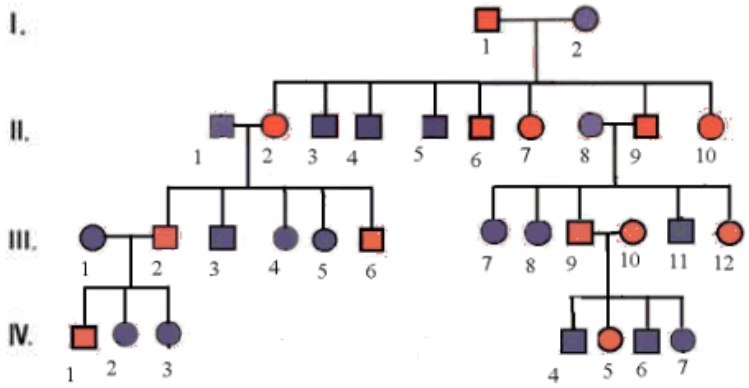
Bicuspid Aortic Valve Is Heritable

Linda Cripe, MD,* Gregor Andelfinger, MD,* Lisa J. Martin, PHD,† Kerry Shooner, MS,*
D. Woodrow Benson, MD, PHD*

1. **Hereditability studies indicate that BAV determination is almost entirely genetic**

2. **Family studies have demonstrated that the pattern of inheritance of BAV is autosomal dominant with incomplete penetrance**

3. **The male predominance and the association of BAV with Turner syndrome suggests an X-linked etiology.**



Evidence in favor of linkage to human chromosomal regions 18q, 5q and 13q for bicuspid aortic valve and associated cardiovascular malformations

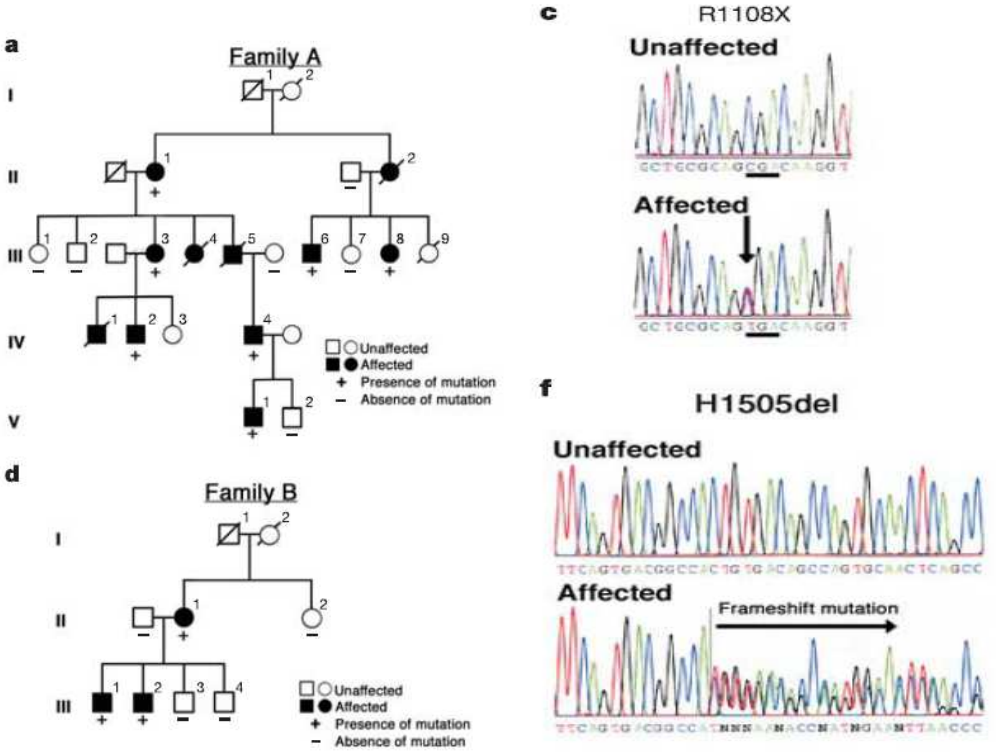
Lisa J. Martin · Vijaya Ramachandran · Linda H. Cripe · Robert B. Hinton · Gregor Andelfinger · Meredith Tabangin · Kerry Shooner · Mehdi Keddache · D. Woodrow Benson

nature Vol 437|8 September 2005|doi:10.1038/nature03940

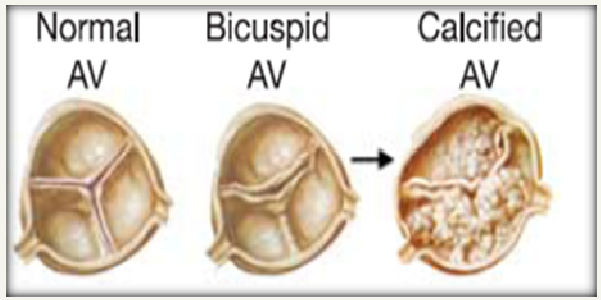
LETTERS

Mutations in *NOTCH1* cause aortic valve disease

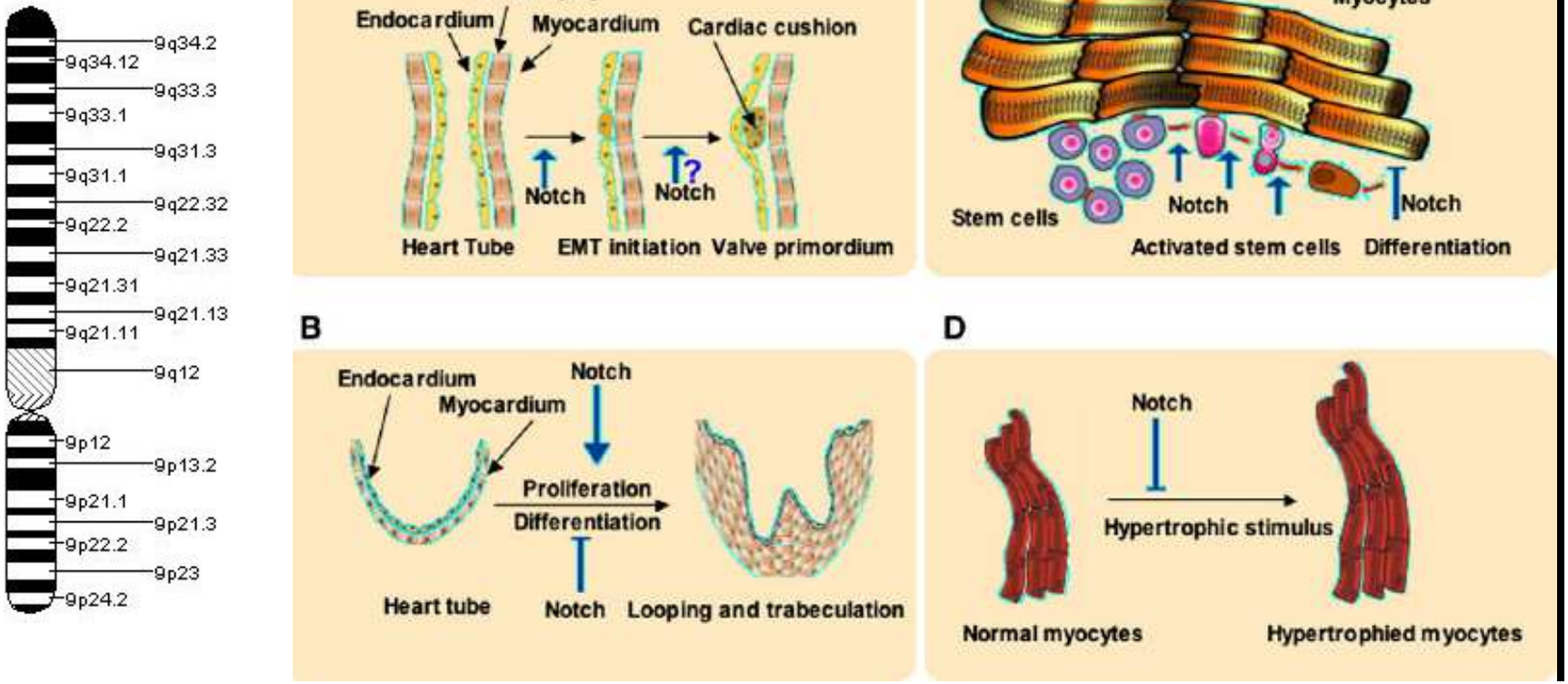
Vidu Garg[1,5], Alecia N. Muth[1]†, Joshua F. Ransom[1]†, Marie K. Schluterman[1], Robert Barnes[3,4], Isabelle N. King[1,5]†, Paul D. Grossfeld[6] & Deepak Srivastava[1,2,4,5]†



***NOTCH1* mutations in 2 families (five generation family) and a second smaller Hispanic family**



NOTCH1



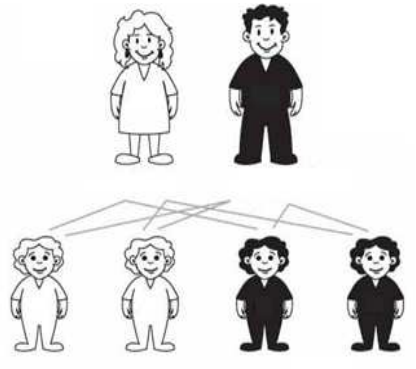
Abnormal Notch signaling leads to valve and septum defects

Aim

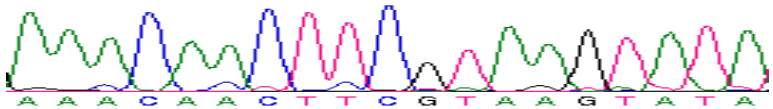
To investigate the role of mutations in *NOTCH1* gene, in patients with familial and sporadic Bicuspid Aortic Valve (BAV).

Study population

11 FAMILIAL CASES



10 SPORADIC CASES



Genetic screening of all 34 coding exons of *NOTCH1* by direct sequencing

Results

Genomic position (NG_007458.1)	Position *NOTCH1* gene	cDNA position (NM_017617.3)	Protein position	Number of patients	rsSNP number (dbSNP)
g.26979 T>C	Exon 3	c.312 T>C	p.N104N	6	rs4489420
g.31330 C>T	Exon 5	c.851C>T	**p.P284L**	1	**New**
g.31331 G>A	Exon 5	c.852 G>A	p.P284P	4	rs2229975
g.34650 T>C	IVS 9-43			3	rs4880099
g.33525A>G	IVS 9+10			2	rs11145767
g.33601 C>A/T	IVS 9+86			2	rs113341997
g.33617C>T	IVS 9+102			1	rs10781498
g.33620C>T	IVS 9+105			1	rs11574887
g.34772C>T	Exon 10	c.1635 C>T	p.D545D	1	rs11574889
g.35062A>G	IVS 11-9			3	rs3124603
g.35367 G>A	IVS 11+63			1	**New**
g.35591C>T	IVS 12+94			1	rs62579232
g.36347G>A	IVS 13+70			2	rs3812609
g.37307 T>C	Exon 14	c.2265 T>C	p.N755N	4	rs2229971
g.39978G>A	IVS 16-4			3	rs3125001
g.40058C>T	Exon 17	c.2664 C>T	p.H888H	1	rs61751548
g.40085C>T	Exon 17	c.2691 C>T	p.A897A	1	rs11574895
g.42820 C>T	Exon 21	c.3498 C>T	**p.G1166G**	1	**New**
g.45953 C>G	Exon 26	c.4856 C>G	**p.Y1619X**	1	**New**
g.47532C>T	Exon 27	c.5094 C>T	p.D1698D	3	rs10521
g.48831 T>C	IVS 30-43			2	rs3124594
g.49928C>T	IVS 30-12			1	rs11574908
g.51487 C>T	IVS 32-41			1	**New**

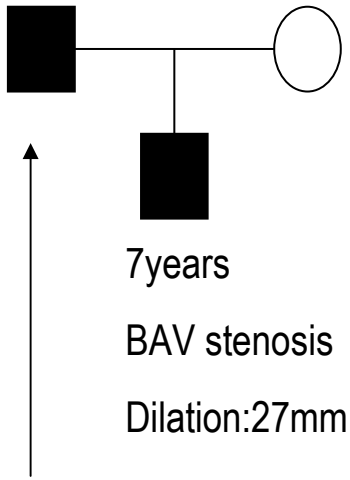
Results

Case 1

40 years

BAV stenosis, calcific valve

Dilation: 48mm



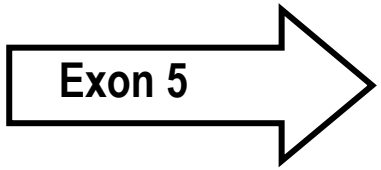
7years

BAV stenosis

Dilation:27mm

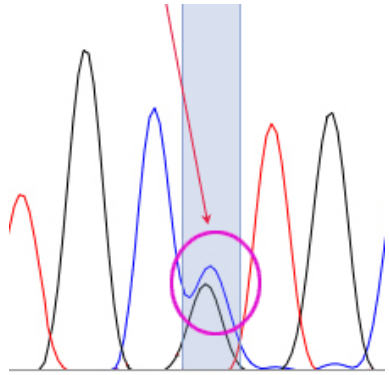
In 2008 38mm

In 2010 48mm



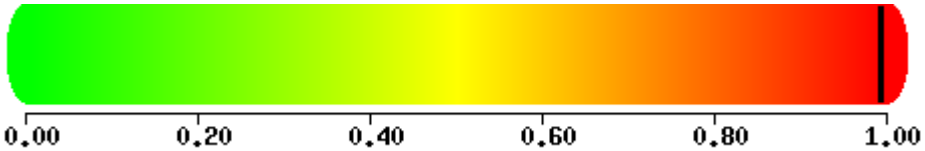
Mutation c. 851 C>T

Pro284Leu



PolyPhen-2 report:

Probably damaging with a score of **0.993**

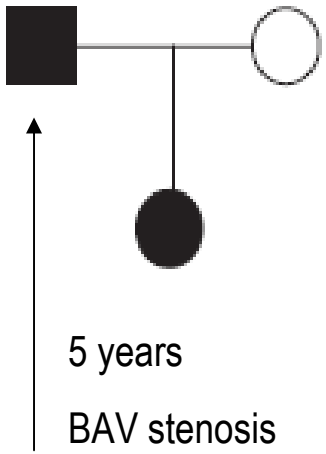


Results

Case 2

38 years

BAV stenosis, CoA



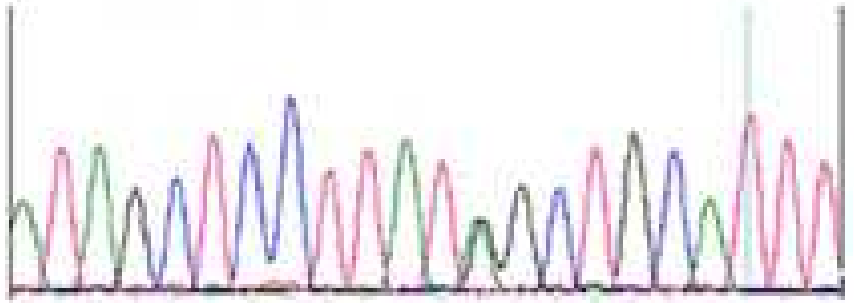
5 years

BAV stenosis

Exon 26

Mutation c. 4856 C>G

Tyrosine1619Stop



Conclusions

- Novel *NOTCH1* mutations in two Italian family with BAV.
- Genetic counseling and clinical care of families presenting with BAV.
- Further studies based on next generation sequencing are needed in order to improve the knowledge of BAV genetics.