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ASSOCIATION OF HYPERTROPHIC CARDIOMYOPATHY PHENOTYPE AND GENOTYPE IN ITALIAN MAINE COON CATS

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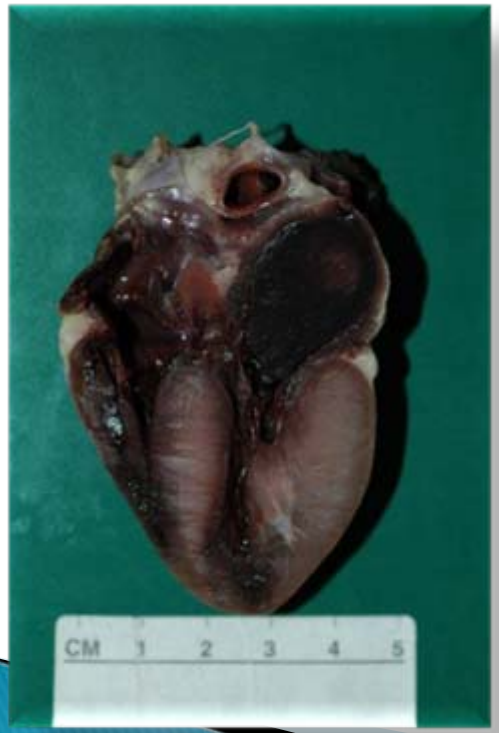
Palais des congrès de Montréal – Montréal, Québec

OVERVIEW

- Hypertrophic Cardimyopathy (HCM; OMIA881/515)
  - most common heart disease in domestic cats
  - Proposed as animal model of the hereditary **human** Familial Hypertrophic Cardiomyopathy (**CMH**; OMIM#192600)
    - CMH is caused by mutations in several **autosomal** (MYH7, TNNT2, TPM1, MYBPC3, TNNI3, MYL2, MYL3, TTN, ACTC1, CAV3, link to 7q31_qter, CSRP3, MYLK2, MYH6) and **mitochondrial** (MTTG; MTTI) genes
    - Mutations can arise independently and can be inherited from a common ancestor

OVERVIEW

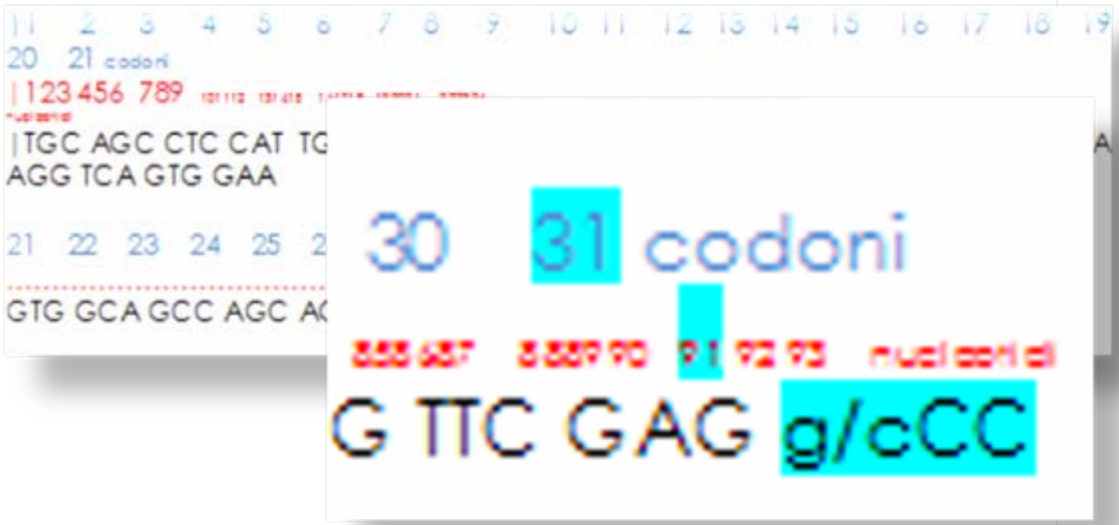
In domestic cats HCM causes heart failure, sudden death, and systemic thromboembolism



OVERVIEW

- Two single nucleotide polymorphisms (SNP) in myosin-binding protein C exon 3 (**MYBPC3**) are associated with the feline HCM:
  - **Maine Coon,** MYBPC3^{G91C}(A31P) (*Meurs et al. Hum Mol Genet. 2005*)
    - 34% of Maine Coon cats worldwide carry this mutation *(Frie et al Vet Intern Med. 2008)*
  - **Ragdoll,** MYBPC3^{C2161T}(R820W) *(Meurs et al. Genomics. 2007)*
  - A second Maine Coon mutation, MYBPC3^{G220A} (A74T) has been proposed, but remains unconfirmed, or discredited *(Nyberg et al Human Genome Meeting – Montreal 2007)*

MYBPC3^{G91C} and MYBPC3^{A31P} is the same mutation



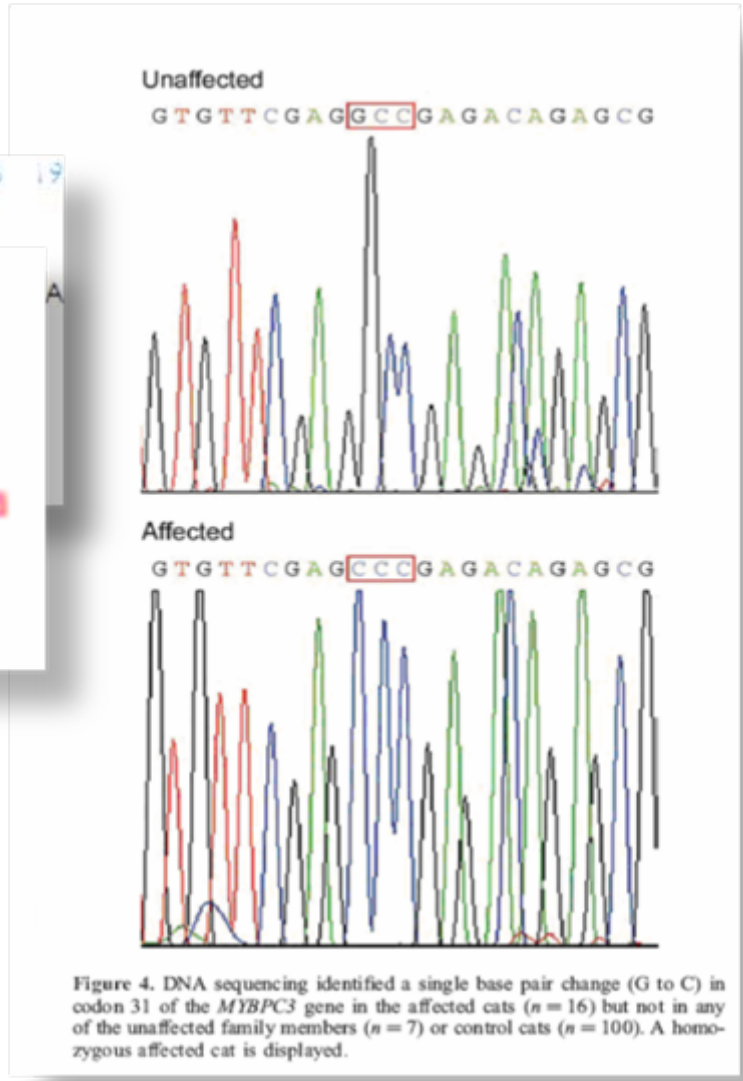
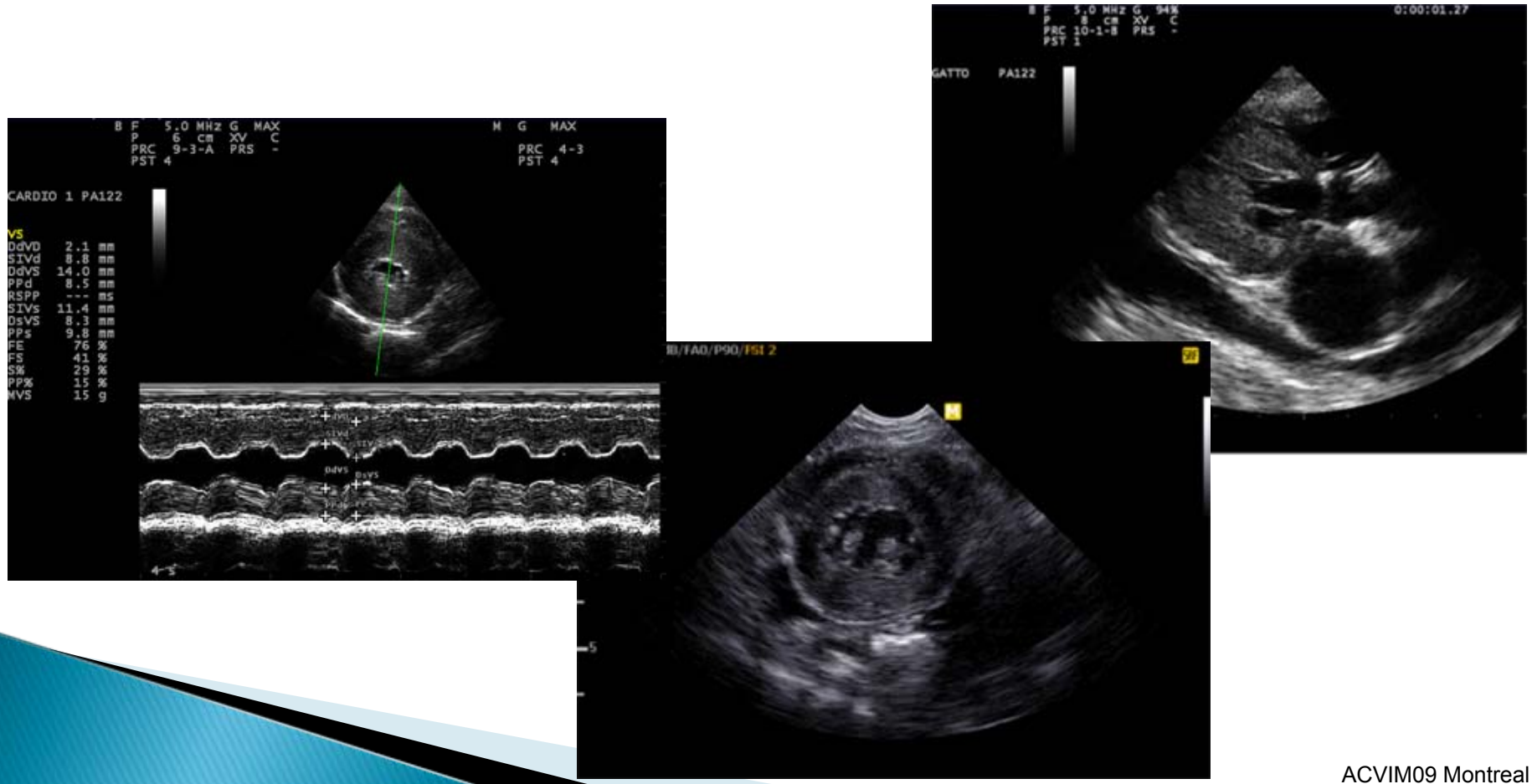


Figure 4. DNA sequencing identified a single base pair change (G to C) in codon 31 of the *MYBPC3* gene in the affected cats ($n = 16$) but not in any of the unaffected family members ($n = 7$) or control cats ($n = 100$). A homozygous affected cat is displayed.

OVERVIEW

Echocardiography remains the gold standard for diagnosis and monitoring of the disease



OVERVIEW

- However, several studies have suggested the relationship between genotype and phenotype is not completely predictable, suggesting additional factors may contribute to the expression of the disease *(Sampedrano et al. JVIM 2009, Wess ACVIM 2008)*

- Several **other breeds and mixed-breed** cats have an increased prevalence of HCM, but the causative mutation(s) have not yet been identified

OVERVIEW

- New genetic tools for inherited disease identification and the possibility of shipping buccal swabs directly from the cattery to diagnostic labs maight circumvet the **veterinary controll** of diagnosis and selection of this disease
- Italian cat breeders belong to one of 6 national feline associations (most important ANFI, AFEF, FIAF) and dozens of fan clubs
- Because of the high prevalence of HCM mutation in Main Coon, a breeding recommendation to eliminate all cats with the mutation could have a **substantial impact on the gene pool**

The Italian Observatory

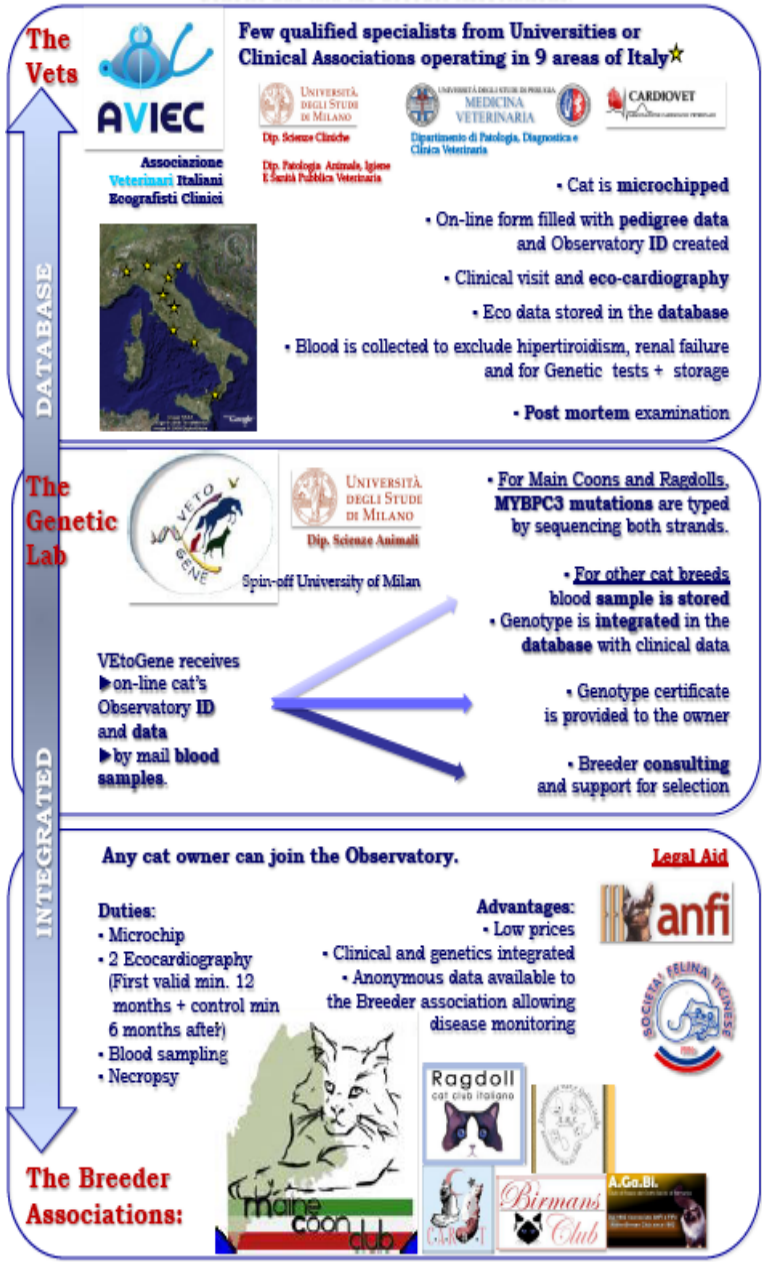
- To overcome the absence of a coherent network the Italian Observatory on Feline Hypertrophic Cardiomyopathy was established in March 2008
- Comprised of
  - **Maine Coon Club and other breed clubs**
  - University of Milano (Spin-off Vetogene)
  - specialist clinicians
- Main aims
  - **Scientific monitoring** of feline inherited disease in Italy (mainly HCM)
  - Assist breeders in breeding decisions
  - Create a **biological bank** and a **database** for further scientific studies
  - **To associate** cat breeders, selected veterinarians and scientific community in Italy

http://www.hcmfelina.com

Osservatorio Italiano HCM Felina

Gruppo di Studio Cardiomiopatia Ipertrofica Felina

- Every breeder or owner can join the observatory
- Every cat included in the Observatory is
  - Microchipped
  - Periodically examined
  - DNA tested for HCM (MC & Ragdolls) and databased
- Results available to
  - Owners
  - Associated Veterinarians
  - Genetic Laboratory
  - Breeder Associations



Any cat owner can join the Observatory.

Duties:

- Microchip
- 2 Ecocardiography (First valid min. 12 months + control min 6 months after)
- Blood sampling
- Necropsy

Advantages:

- Low prices
- Clinical and genetics integrated
- Anonymous data available to the Breeder association allowing disease monitoring

Legal Aid

The Breeder Associations:

C.A.R.a.T

Ragdoll cat club italiano

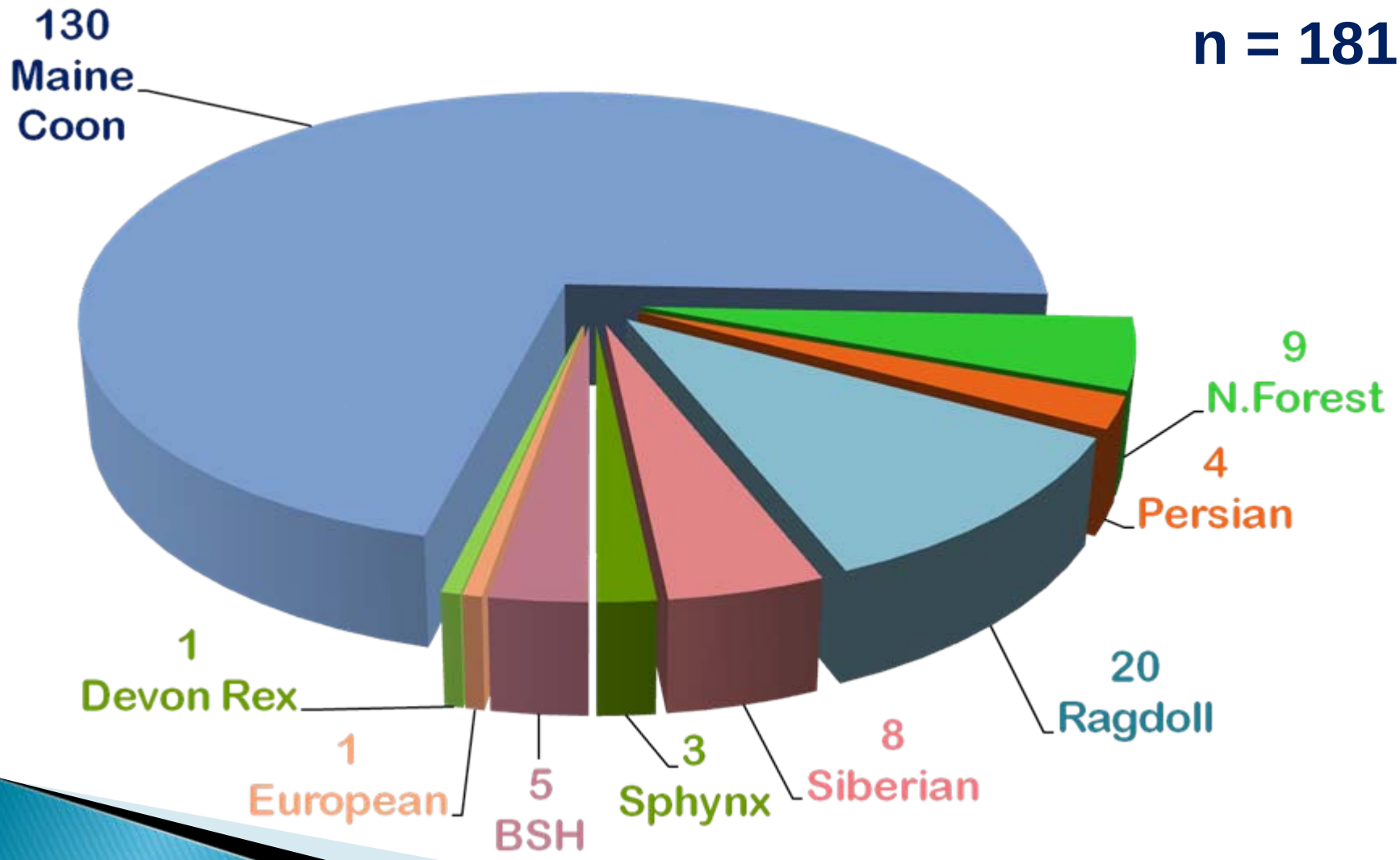
Associazione Rex e Sphynx Italia A.R.S. http://www.rexsphynx.com

SOCIETA' FELINA TICINESE 1910

A.Ga.Bi. Club di Razza del Gatto Sacro di Birmania
Dal 1982 riconosciuto ANFI e FIFe
Italian Birman Club since 1982

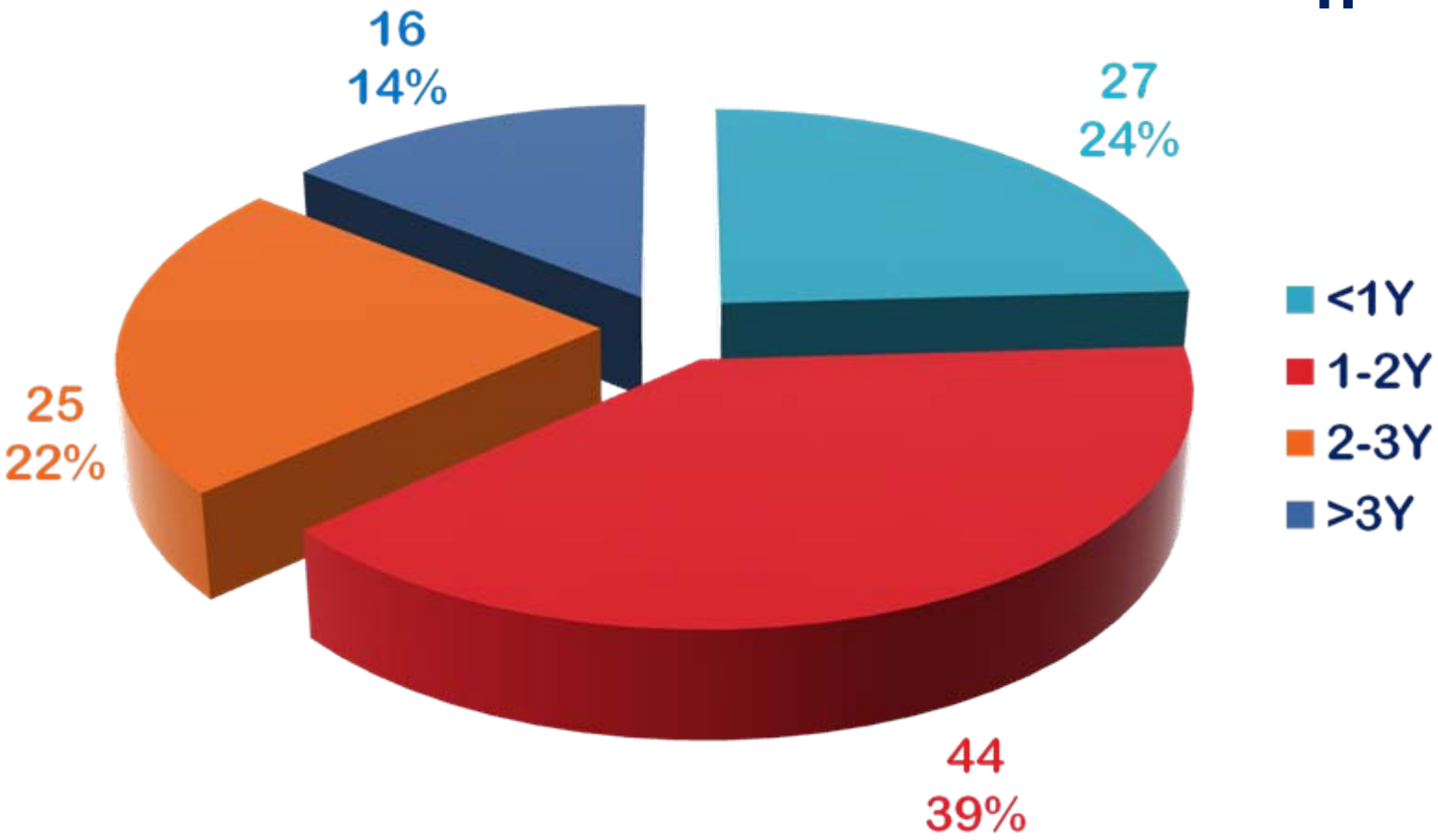
Birmans Club

Demographics by Breed



Demographics by Age

n = 112



Echocardiographic examination

- Conventional 2D and M-mode evidence left ventricular concentric hypertrophy
- End diastolic thickness of Interventricular Septum (IVS) or Left Ventricular Posterior Wall (LVPW) >6mm (5.5-6mm were considered borderline values)

Echocardiographic classification

Thickness of LVFW and/or IVS

wall thickness ≥ or < 6mm respectively

positive ⟷ **negative**

Severity of HCM is classified *by the Observatory* in border line, **mild**, **moderate** and **severe** by considering other echocardiographic parameters

Echocardiographic classification

LVFWd and/or IVSd (mm)	results	HCM	*recheck*
< 5.5	normal	**negative**	*12 months*
> 5.5 and < 6.0	questionable	**borderline**	*6 months*
> 6.0 and < 6.5	pathologic	**mild**	*6 months + t4 creatinine and BUN*
> 6.5 and < 7.0	pathologic	**moderate**	*6 months + t4 creatinine and BUN*
> 7.0	pathologic	**severe**	*1-3 months + t4 creatinine and BUN*

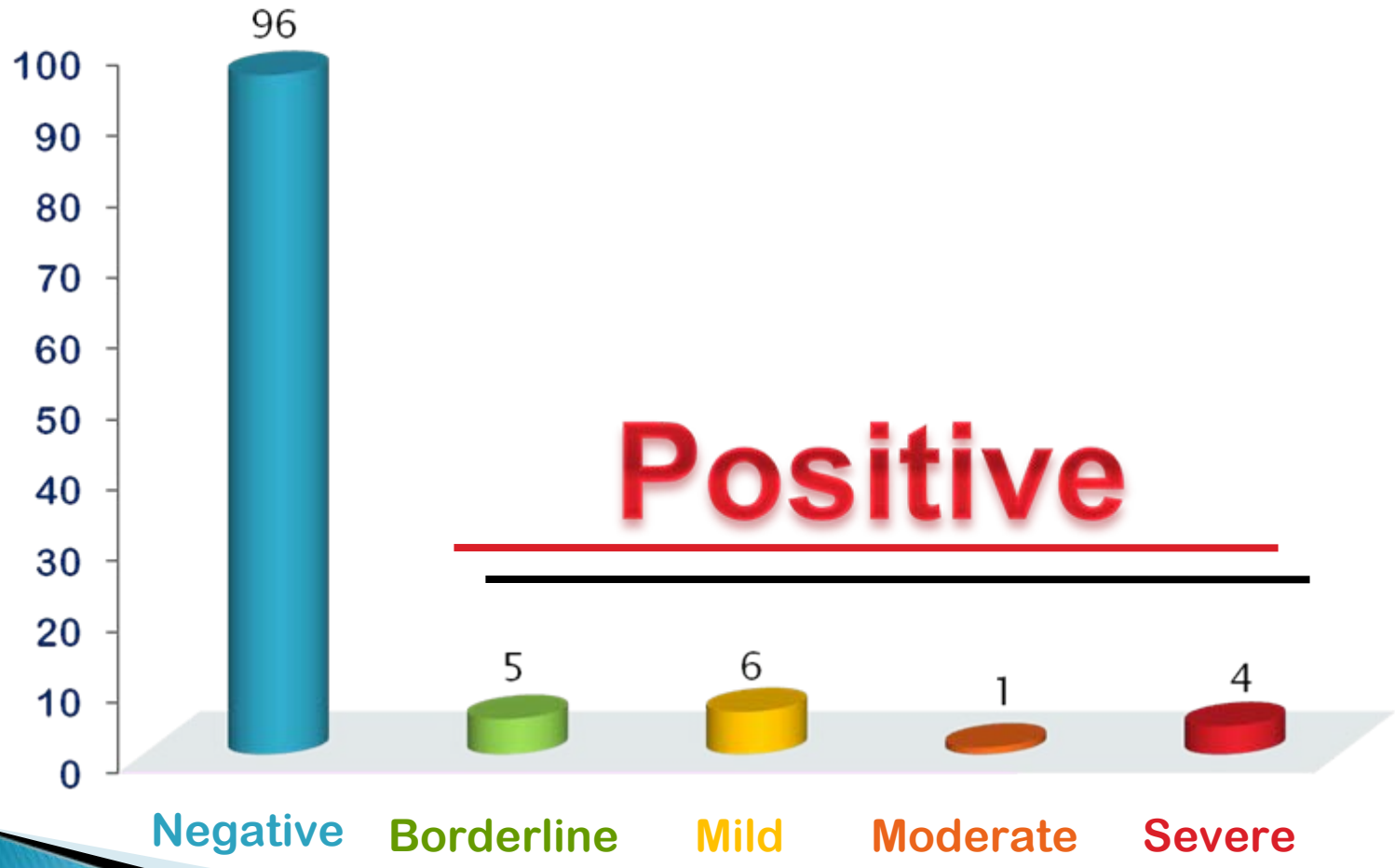
Necropsy is performed in every case in accordance with an agreement among the OBSERVATORY, Breeders, Fan Clubs and Owners

Echocardiographic examination

- Severity of HCM is classified *by the Italian Observatory* as **severe even if the wall thickness is >6.5 but <7 mm but at least one of the following conditions is present**
  - Systolic left ventricular chamber obliteration
  - Presence of dynamic obstruction (SAM and Mid-ventricular obstruction)
  - Left atrial enlargement
  - Presence of thrombus (intraluminal and spontaneous echo contrast)

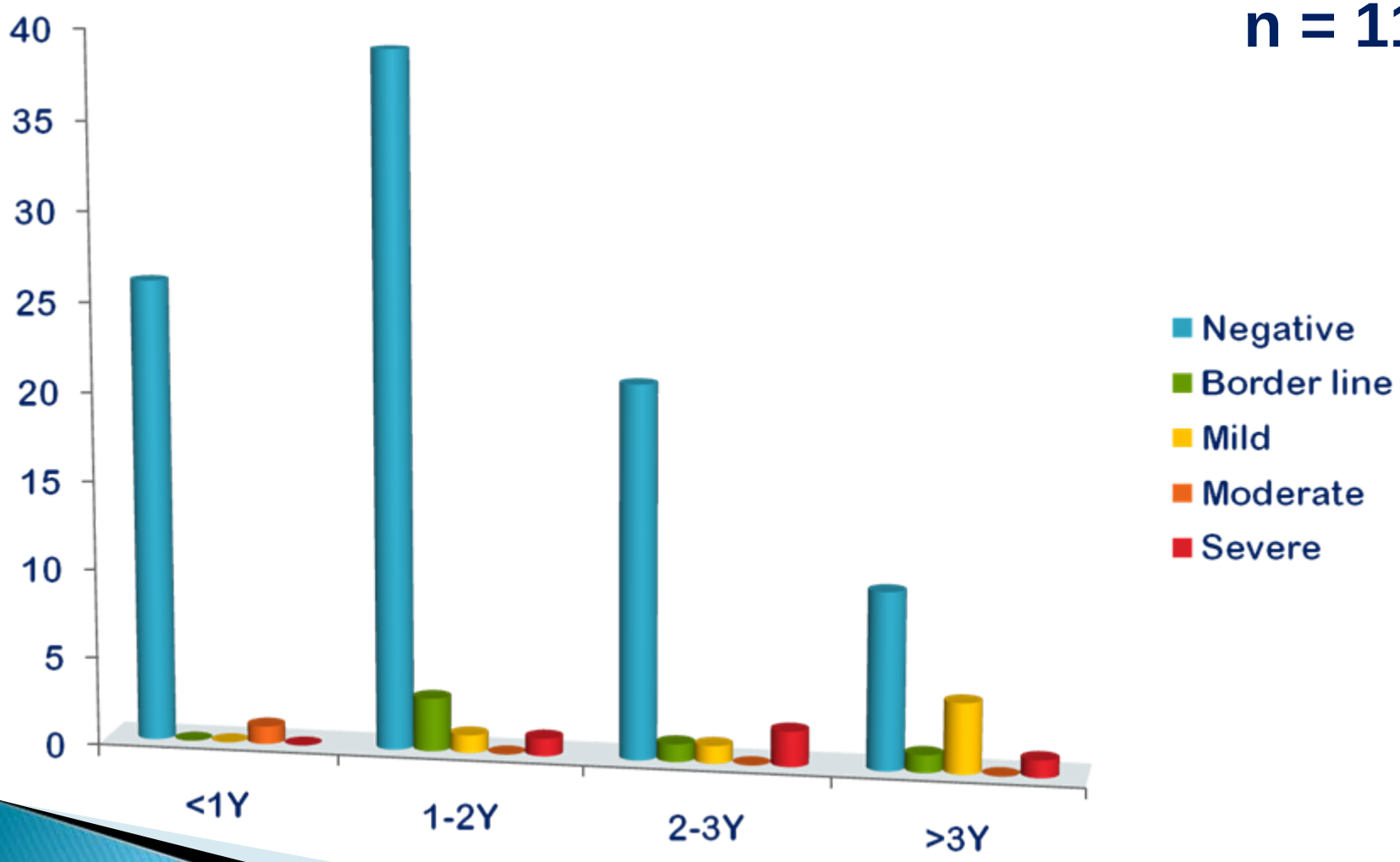
Echocardiographic results

n = 112



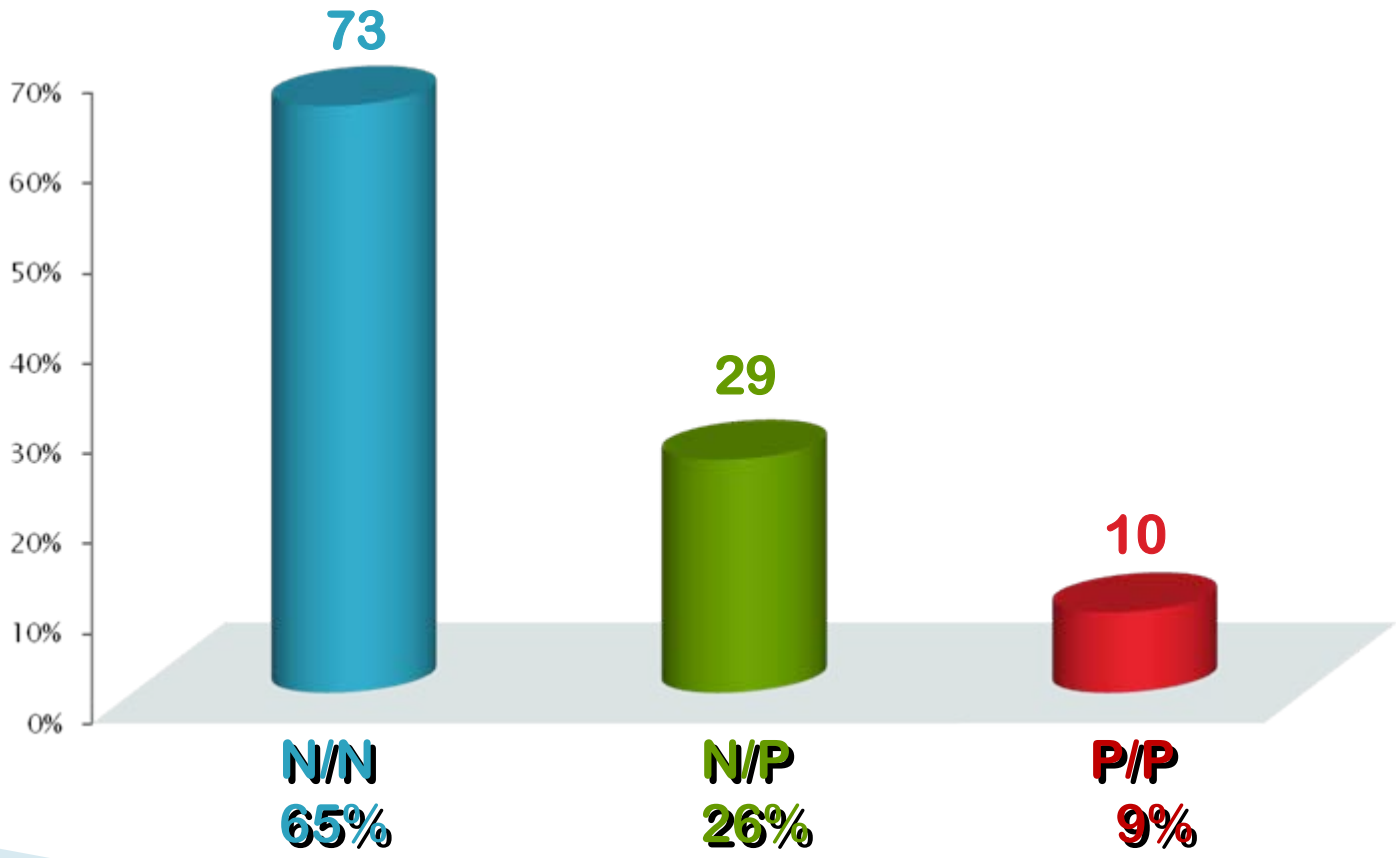
Echocardiographic results

n = 112



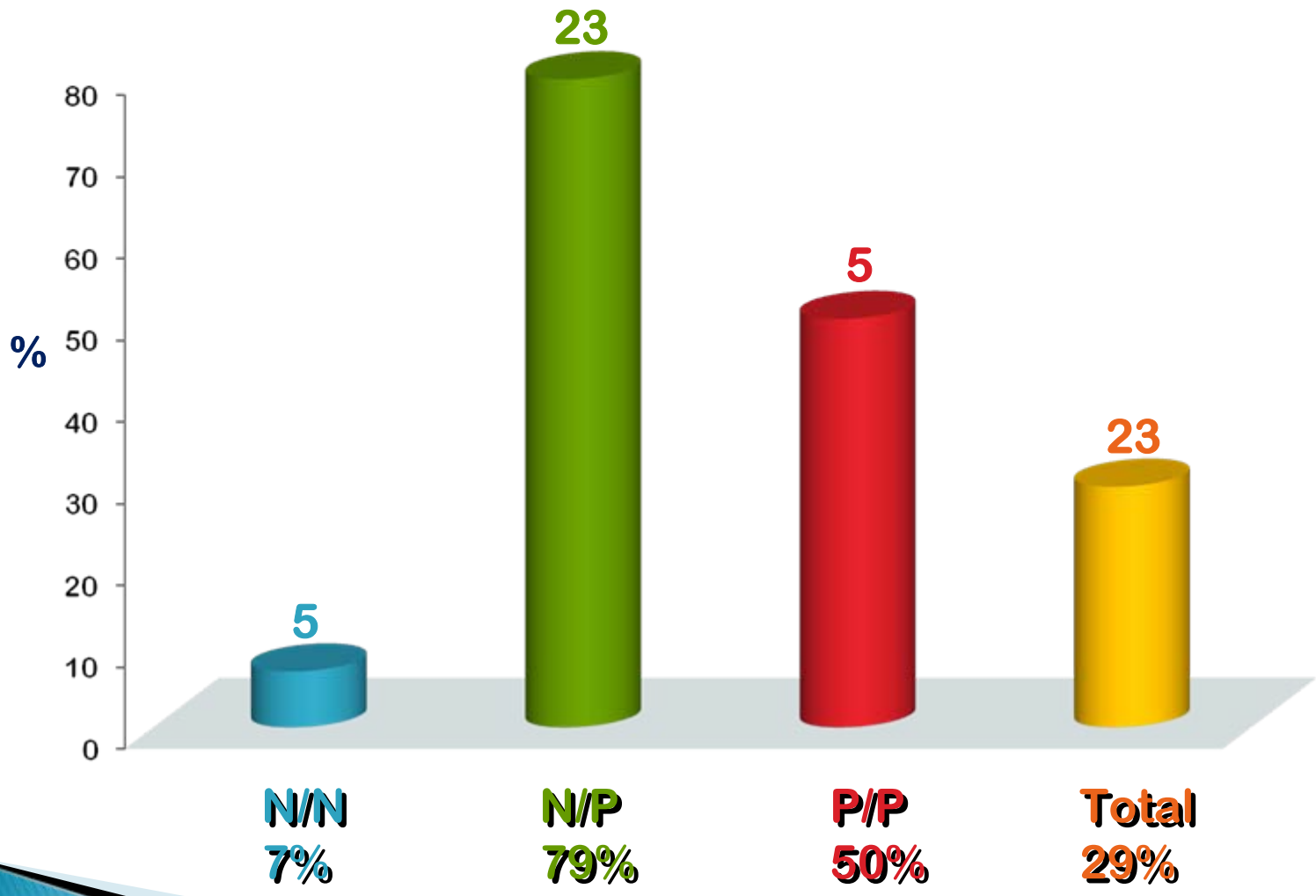
Genotyping results MyBPC3^{A31P}

n = 112



Genotype and phenotype discordance

Genotype-phenotype discordance



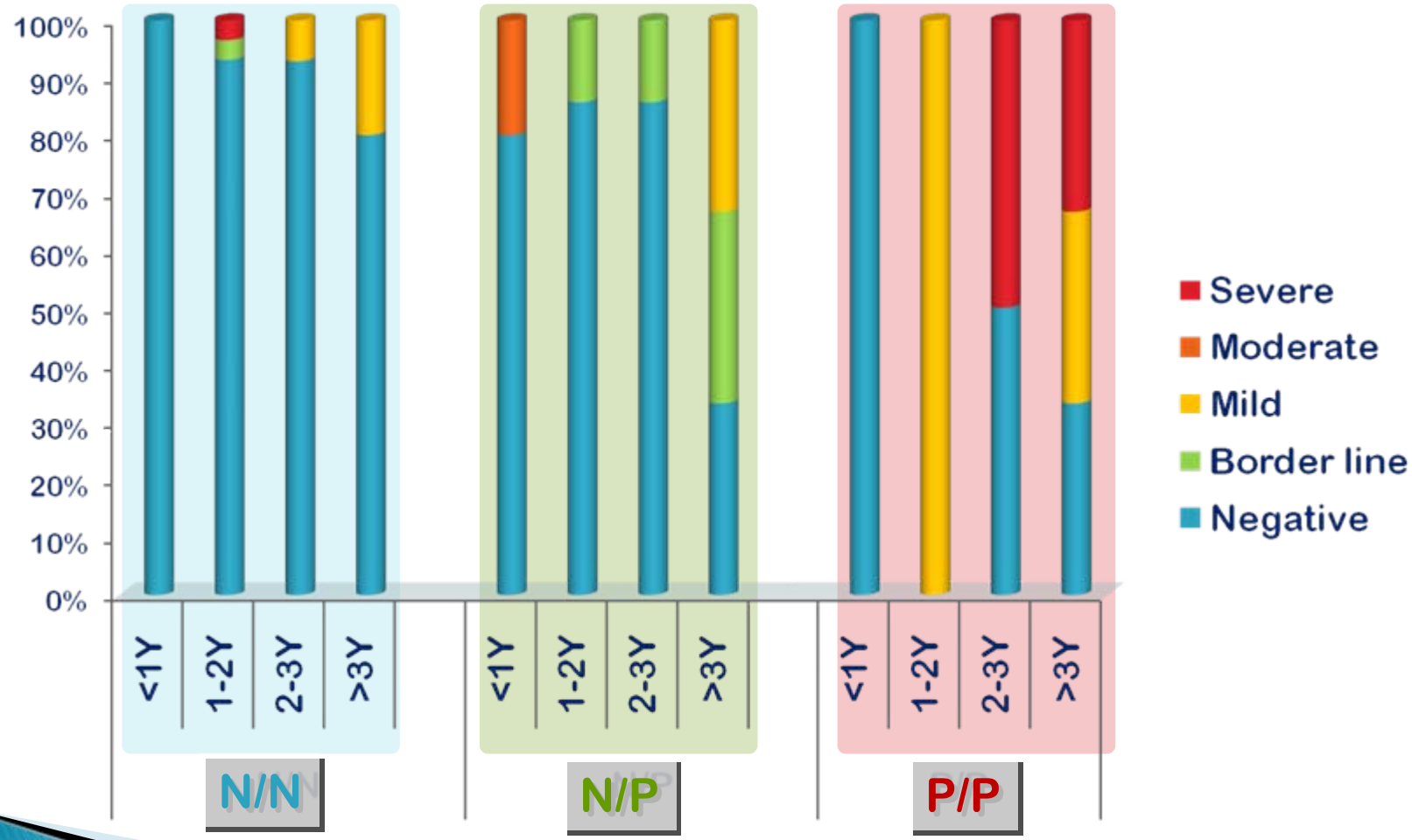
Results

Average discrepancy between genetic and echocardiographic results was 29% with most discrepancy (79%) associated with the P/N genotype

BUT…!!

(In Italy we say that there is always a "BUT")

Genotype-phenotype discordance by Age



Results

- In cats >3 years, only 1of the 10 echo-negative cats had a P/N genotype and only 1 had a P/P genotype
- However, the incidence of echo-positive cats with N/N genotype increased from 0% to 20% with increasing age

Discussion

- Our study demonstrates substantial discordance between genotype and phenotype in heterozygous Italian Maine Coons <3 years of age
- Construction of age-specific detection curves for P/N and P/P genotypes is necessary to calculate the probability that asymptomatic subjects will develop the disease
- The presence of some echo-positive cats with a N/N genotype indicates that factors other than the MYBPC3 G91C mutation are likely involved in HCM in Maine Coons

Limitations

- Relatively few cats >3years – data are not robust at this time
- Echo criteria relatively simple and may not completely accurately classify HCM severity
- Echo criteria are based on adult assessment and may not apply to juvenile cats

Future Directions

- 2008 is the first year of the Observatory
  - Data will be collected over several years (5-10)
  - Hope to enroll >1000 cats
  - Examine the natural history of the disease prospectively
  - Examine potential risk factors in clinical outcomes (FATE, CHF)
  - Examine rationale of breeding decisions based on genotypic analysis alone – should all N/P cats be excluded from the gene pool, or should this be restricted to P/P cats?

Genetically P/P–Echo Positive–severe HCM class

"Napoleone" The young premature death

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