

session 38, abstract number 1214

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A novel approach for estimating allele frequencies of lethal autosomal-recessive genetic disorders



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Introduction



- * 1,830,125 records of BS in Austria
- * 4 lethal autosomal recessive genetic disorders
 - Arachnomelia (A)
 - Spinal Dysmyelination (SDM)
 - Spinal Muscular Atrophy (SMA)
 - Weaver (W)

	Number of carriers
A	11
SDM	16
SMA	78
W	77

Aim



**To estimate lethal allele frequencies
in reference populations
using 3 different methods.**

**Method 1. Gene counting (Deterministic method)
(Lidauer and Essl., 1994)**

**Method 2. Probability of gene origin (Deterministic method)
(Man *et al.*, 2007)**

**Method 3. Adaptation of gene dropping approach
(stochastic method)**

Method 1. Gene counting

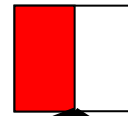


- * **Proposed by Allaire *et al.*, 1982**
- * **Summarize gene frequencies in known ancestral genotypes weighted by the probability that these genes are transmitted to the individual**
- * **Six generations from carrier to the reference population are considered (Lidauer and Essl., 1994)**

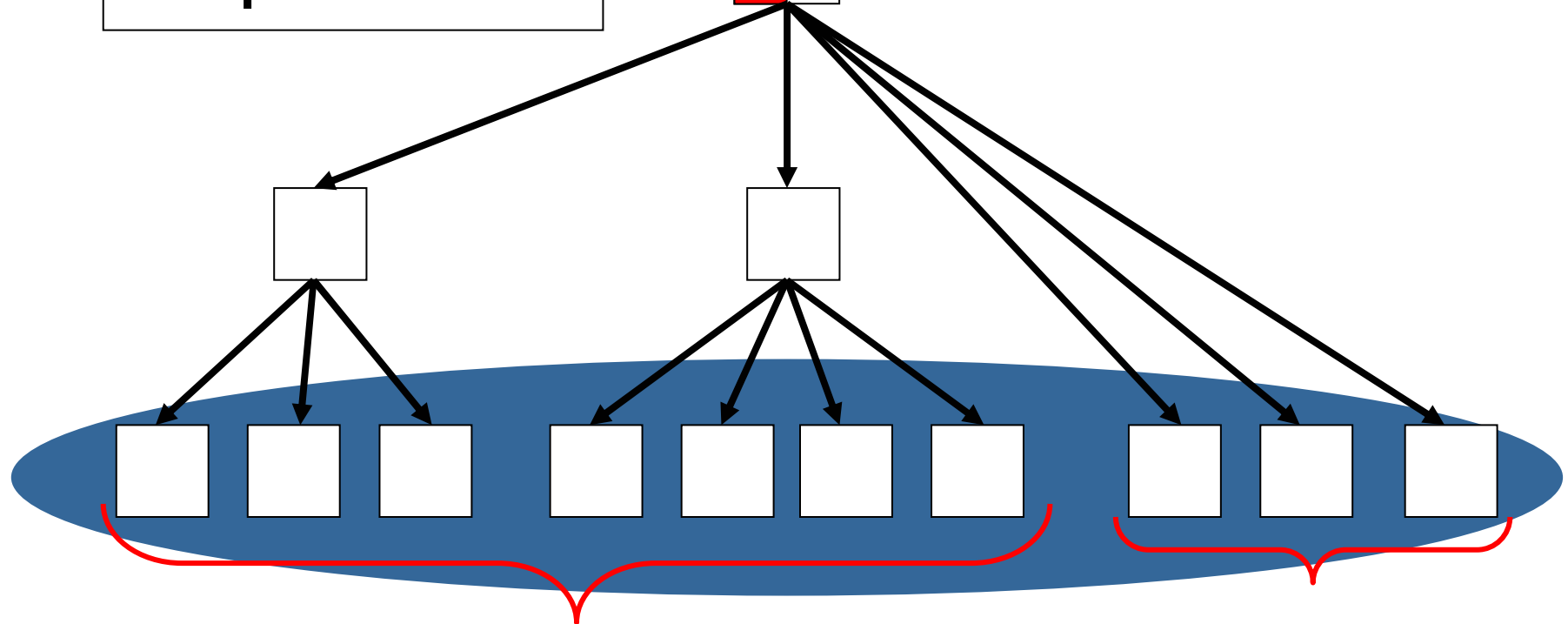
Method 1. Gene counting

$$q = \sum_i (0.5)^{n_i} * f_i$$

Carrier: sire or grandsire



Lethal allele freq. = 0.5



$$= \frac{7 * ((0.5)^2 * 0.5) + 3 * ((0.5)^1 * 0.5)}{7 + 3}$$

$$= 0.1625$$

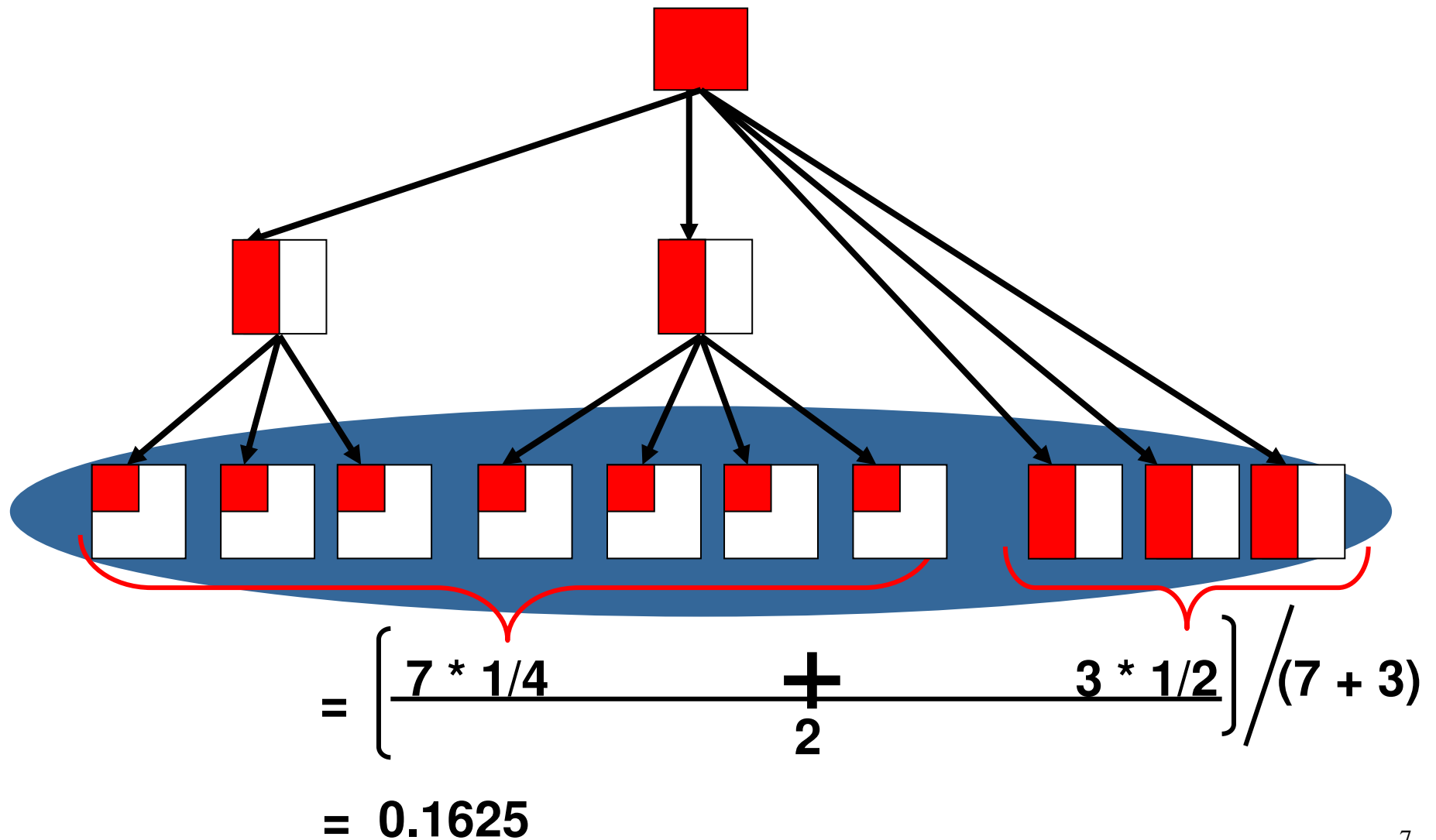
Method 2. Probability of gene origin



- * **Proposed by Man *et al.*, 2007**
 - * **Marginal/total gene contribution (Boichard *et al.*, 1997)**
 - * **Expected lethal allele freq.**
- 1 carrier $\longrightarrow$ $\frac{1}{2}$ Total gene contribution**
- > 1 carrier $\longrightarrow$ $\frac{1}{2} \Sigma$ Marginal gene contribution**

Method 2. Probability of gene origin

Carrier: sire or grandsire



Method 3. Adaptation of gene dropping approach

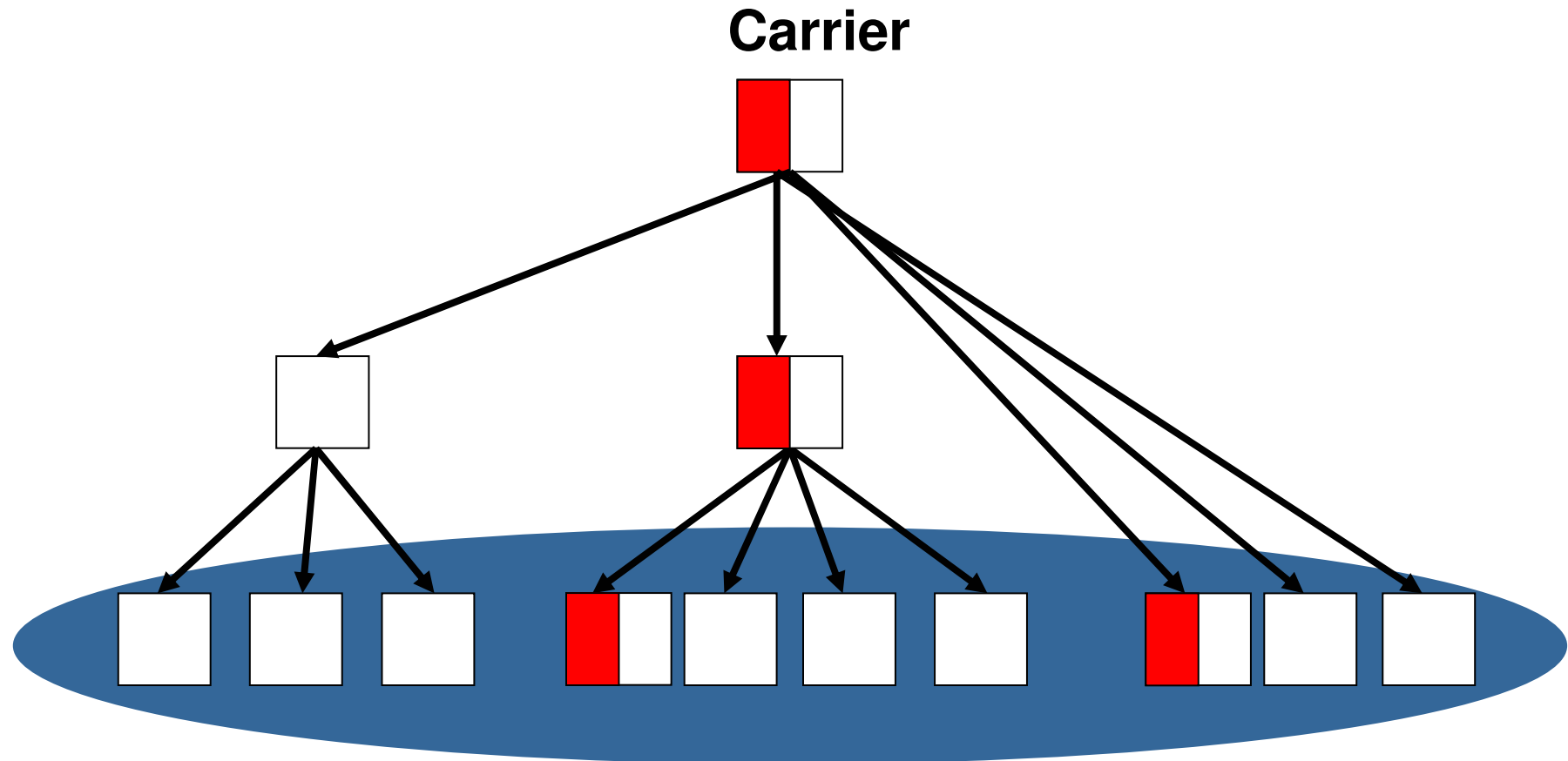


*** Proposed by MacCluer *et al.*, 1986**

*** Principles**

- 1. Each carrier has one normal and one lethal allele**
- 2. Lethal alleles are flagged**
- 3. Alleles are dropped through a pedigree**
- 4. 50:50 transmission probabilities, no mutation**
- 5. Avoid overestimation**
 - if a descendent inherited 2 lethal alleles, the gene dropping procedure is repeated.**

Method 3. Adaptation of gene dropping approach



1 runs = $2/20 = 0.10$

1,000 runs = 0.1625

Result (1) Comparison of allele frequencies



Diseases	Ref.	Gene counting	Probability of gene origin	Gene dropping
A	2001	1.08	2.24	2.11
	2005/6	0.93	2.44	2.32
SDM	2001	4.88	7.46	7.03
	2005/6	5.58	8.95	8.32
SMA	2001	5.80	9.48	8.94
	2005/6	6.49	11.03	10.24
W	2001	3.75	5.77	5.51
	2005/6	2.84	4.58	4.44

Result (1) Comparison of allele frequencies



Diseases	Ref.	Gene counting	Probability of gene origin	Gene dropping
A	2001	1.08	2.24	2.11
	2005/6	0.93	2.44	2.32
SDM	2001	4.88	7.46	7.03
	2005/6	5.58	8.95	8.32
SMA	2001	5.80	9.48	8.94
	2005/6	6.49	11.03	10.24
W	2001	3.75	5.77	5.51
	2005/6	2.84	4.58	4.44

Result (1) Comparison of allele frequencies



Disease	Ref.	Gene counting	Probability of gene origin	Gene dropping
A	2001	1.08 ↓	2.24 ↑	2.11 ↑
	2005/6	0.93	2.44	2.32
SDM	2001	4.88 ↑	7.46 ↑	7.03 ↑
	2005/6	5.58	8.95	8.32
SMA	2001	5.80 ↑	9.48 ↑	8.94 ↑
	2005/6	6.49	11.03	10.24
W	2001	3.75 ↓	5.77 ↓	5.51 ↓
	2005/6	2.84	4.58	4.44

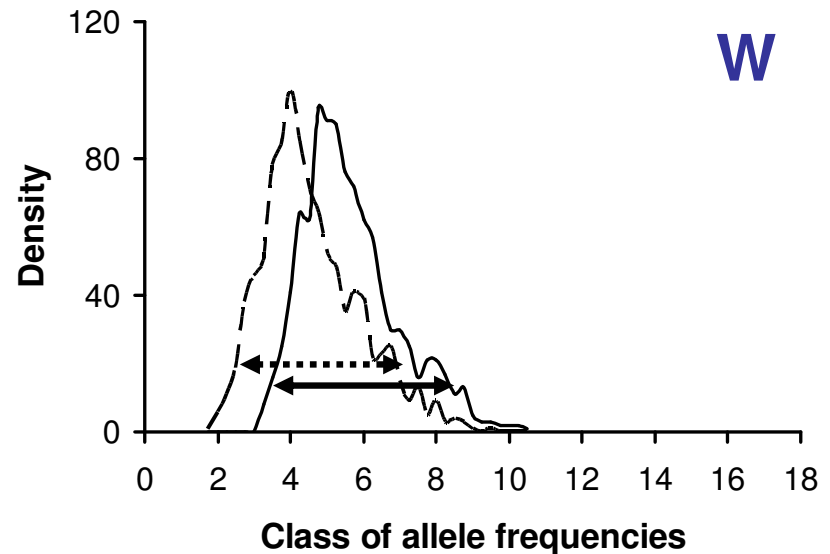
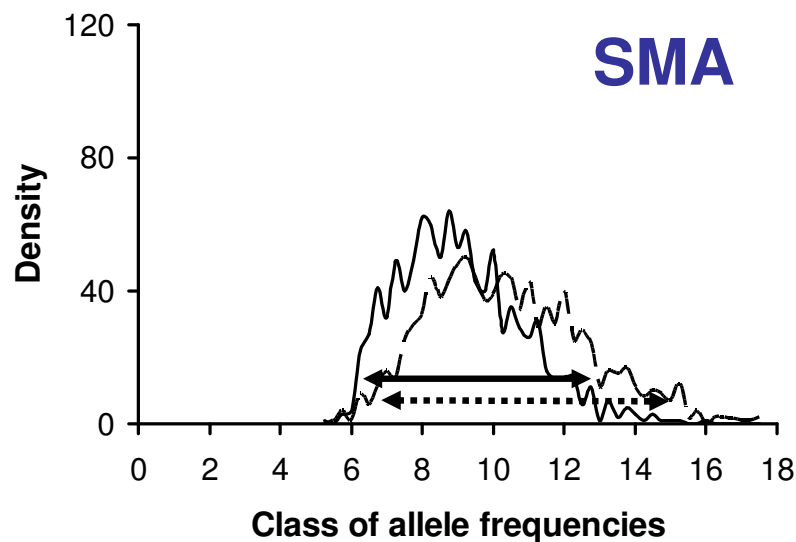
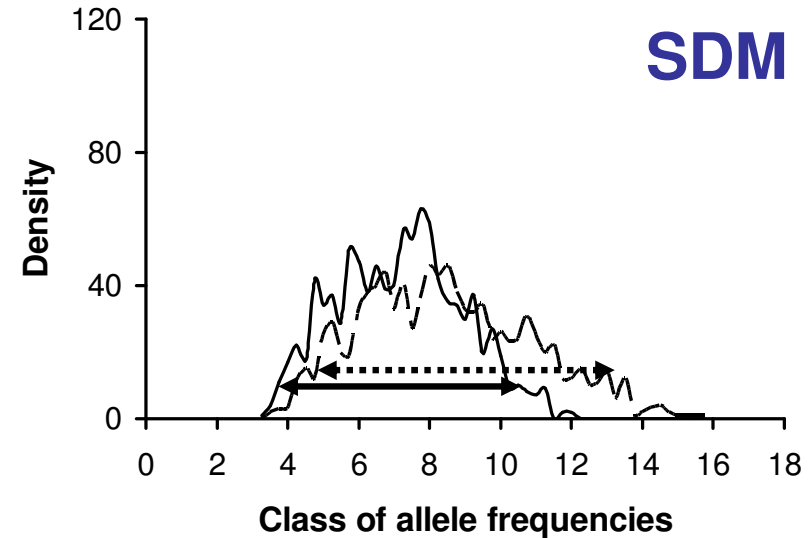
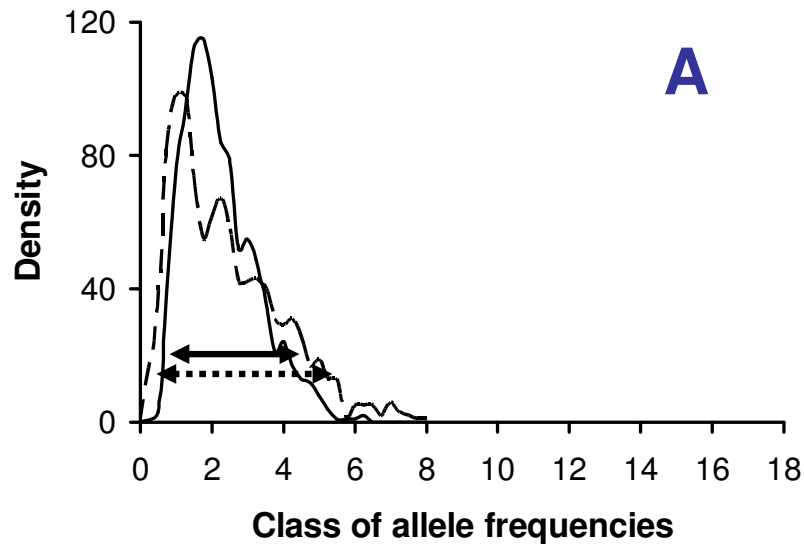
Result (2) SD & 95% CI (Gene dropping)



Diseases	Ref.	Mean	SD	95% CI
A	2001	2.11	1.02	0.67 – 4.63
	2005/6	2.32	1.49	0.46 – 5.60
SDM	2001	7.03	1.77	3.86 – 10.61
	2005/6	8.32	2.37	4.30 – 13.17
SMA	2001	8.94	1.76	6.19 – 12.96
	2005/6	10.24	2.19	6.64 – 15.03
W	2001	5.51	1.31	3.51 – 8.61
	2005/6	4.44	1.34	2.36 – 7.54

Result (3) Distribution of alleles frequencies in 2 ref.

—— Ref. 2001, - - - - Ref. 2005/6, Arrow : 95% CI



Summary



- 1. Gene counting → lower estimates**
- 2. Results of adapted gene dropping approach are similar to results for probability of gene origin.**
- 3. Adaptation of gene dropping**
 - Distribution**
 - SD, 95% CI**
- 4. Large complex pedigree**



**Thank you
for your attention**

