IS THERE ANY GENOTYPE – PHENOTYPE RELATIONSHIP IN PATIENTS WITH HEREDITARY ANGIOEDEMA?

T. Freiberger

Molecular Genetics Lab, Centre for Cardiovascular Surgery and Transplantation, Brno, CR

Centre for Primary Immunodeficiencies, Masaryk University Brno, CR

Hereditary angioedema

CLINICS

- potentially life-threatening
- recurrent localized edema of the skin or of the mucosa of GIT or larynx
- age of onset variable; frequently worsening around puberty
- attacks often triggered by minor trauma or stress

- AD inheritance; 1:10-50 000

Hereditary angioedema

LABORATORY FINDINGS

- low C4 (C4d), C2
- C1 inhibitor deficiency
  - type I (85%) – low C1 INH ag (5-30%), low C1 INH function
  - type II (15%) - normal C1 INH ag, low C1 INH function
  - (type III? – rare? – familial, estrogen dependent, only females, both C1 INH ag and function normal)

Hereditary angioedema

C1 INHIBITOR GENE

- 11q11-q13
- 8 exons; > 17 kb; 478 AA
- high number of *Alu* repetitive regions → large deletions, duplications (about 20% of all mutations)
- > 100 mutations described
  - 20% de novo mutations

Hereditary angioedema

BIOLOGIC ROLE OF C1 INH

- regulator of complement, contact, coagulation and fibrinolytic systems
  - primary and only inactivator of C1r and C1s
  - inactivates MASPs
  - regulates generation of bradykinin (inactivation of plasma kallikrein and factor XIIa)
  - …

GENOTYPE-PHENOTYPE RELATIONSHIP

GENETIC FACTORS POTENTIALLY INFLUENCING CLINICAL MANIFESTATION OF HAE

- C1 INH gene

GENOTYPE-PHENOTYPE RELATIONSHIP

C1 INH GENE

- ! phenotype highly variable even among members of the same family, i.e. carriers of the same C1 INH mutation!
  - different severity, age of onset, frequency of attacks

GENOTYPE-PHENOTYPE RELATIONSHIP

C1 INH GENE

- type of C1 INH mutation associated rather with laboratory phenotype than clinical manifestation
  - *missense* mutation in the reactive center loop - 75% patients with HAE type II
  - *large deletions*, *nonsense*, *frameshift* and *splicing* mutations – causal usually in HAE type I
  - *inframe del/ins*, *missense* mutations outside of reactive center loop – need functional assays to prove their causal influence – HAE type I, II
- lack of correlation of particular mutation with clinical phenotype

GENOTYPE-PHENOTYPE RELATIONSHIP

- it is thus clear that HAE phenotype is influenced by some other factors than mutations in C1 INH gene

HAE patients

- 37 patients (19 kindreds)
  - highly variable phenotype even among family members justifies involvment of relatives in this study
- sorted

  according to the disease severity
  - severe course - the history of laryngeal edema or ileus;
  - intermediate course - other symptoms of HAE requiring hospitalisation
  - mild course - symptomatic patients without the need for hospitalisation

  according to the age of clinical symptoms onset
  - prepubertaly; < 13
  - ≥ 13

  according to the frequency of attacks
  - < 12 per year
  - 12-24 per year
  - > 24 per year

GENOTYPE-PHENOTYPE RELATIONSHIP

GENETIC FACTORS POTENTIALLY INFLUENCING CLINICAL MANIFESTATION OF HAE

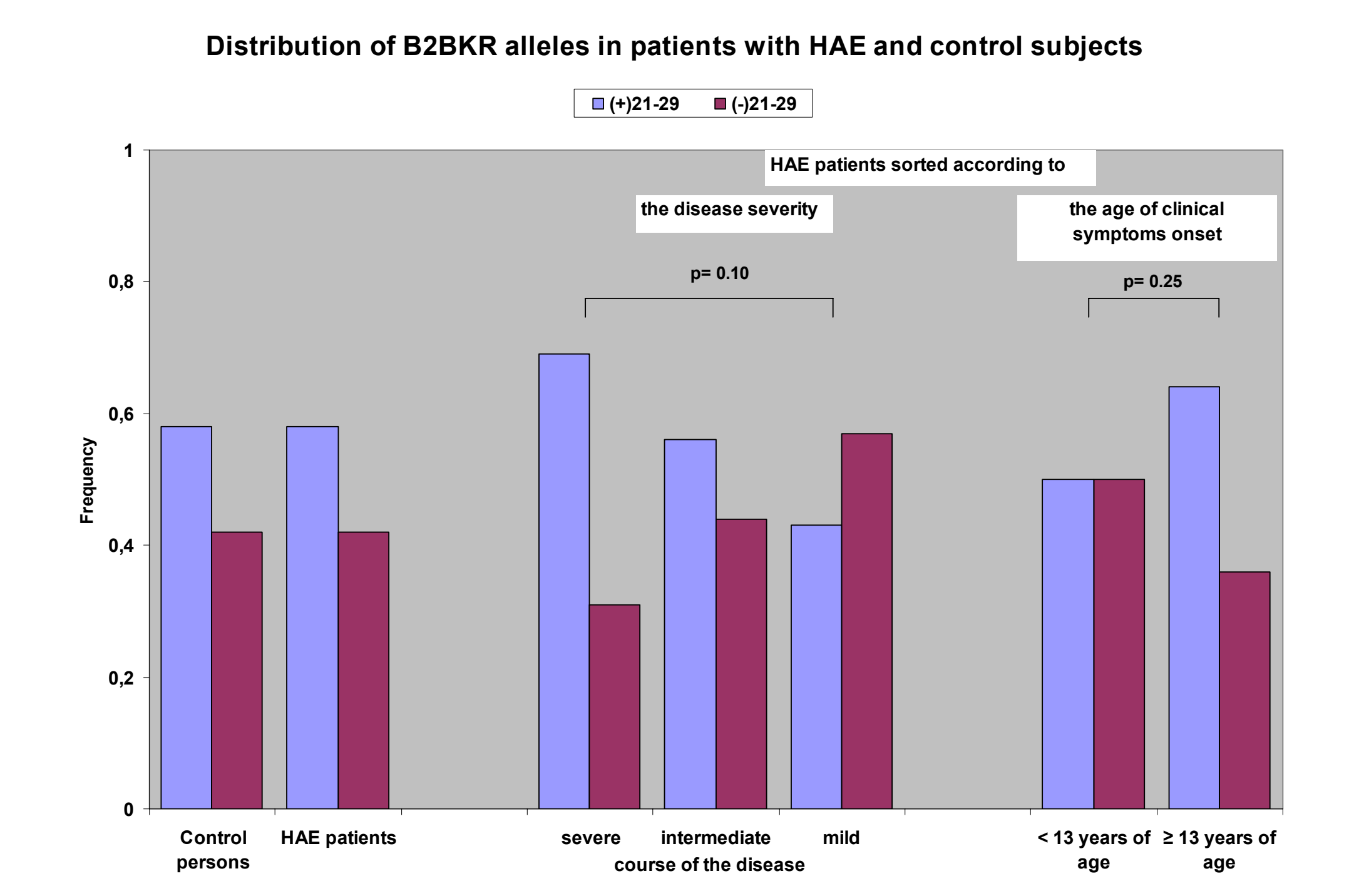
- C1 INH gene
- BRADYKININ RECEPTOR gene
  - bradykinin – hypothesized to be a primary mediator of edema in C1 INH deficiency
    - increased in plasma during attacks
    - increased vascular permeability in C1 INH deficient mouse reversed by bradykinin receptor antagonist

GENOTYPE-PHENOTYPE RELATIONSHIP

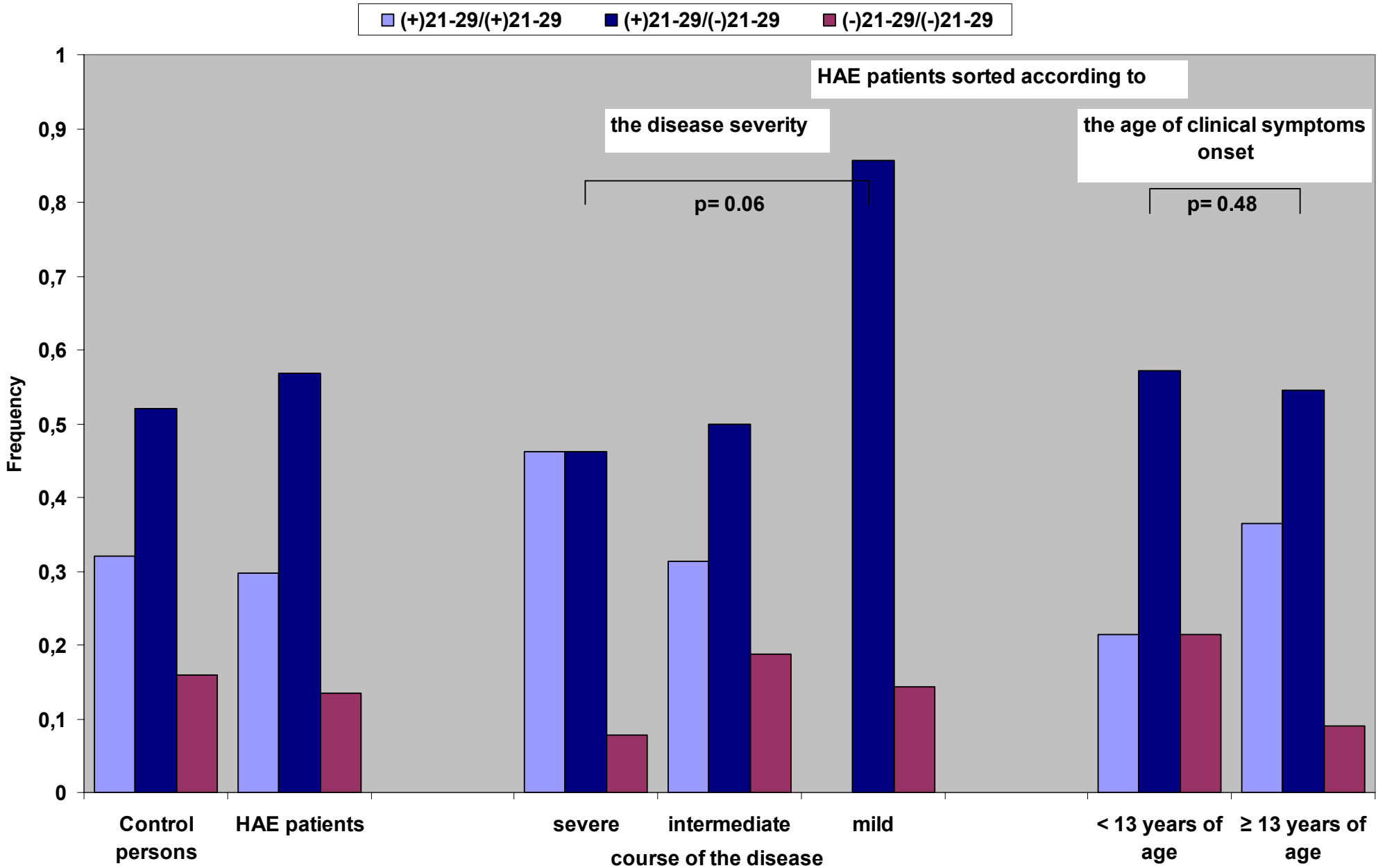
BRADYKININ RECEPTOR GENE – B2BKR

- polymorphic variant (9 bp deletion; $(-)^{21-29}$) in the B2BKR gene was found to be increasingly expressed (in comparison to variant without deletion)
- $(-)^{21-29}$ variant facilitates edema manifestation in HAE patients

(Lung; JACI 1997)


Distribution of B2BKR alleles in patients with HAE and control subjects
(+)21-29
(-)21-29
HAE patients sorted according to
the disease severity
the age of clinical symptoms onset
p= 0.10
p= 0.25
Frequency
1
0,8
0,6
0,4
0,2
0
Control persons
HAE patients
severe
intermediate
mild
course of the disease
< 13 years of age
≥ 13 years of age

Distribution of B2BKR genotypes in patients with HAE and control subjects



GENOTYPE-PHENOTYPE RELATIONSHIP

BRADYKININ RECEPTOR GENE – B2BKR

- Lung et al.: $(+)^{21\text{-}29}/\ (+)^{21\text{-}29}$ genotype only in controls and asymptomatic HAE patients
- our study: $(+)^{21\text{-}29}/\ (+)^{21\text{-}29}$ genotype in 11 symptomatic patients; 1 asymptomatic patient: $(+)^{21\text{-}29}/\ (-)^{21\text{-}29}$

- other polymorphisms in the B2BKR gene and/or other genes involved

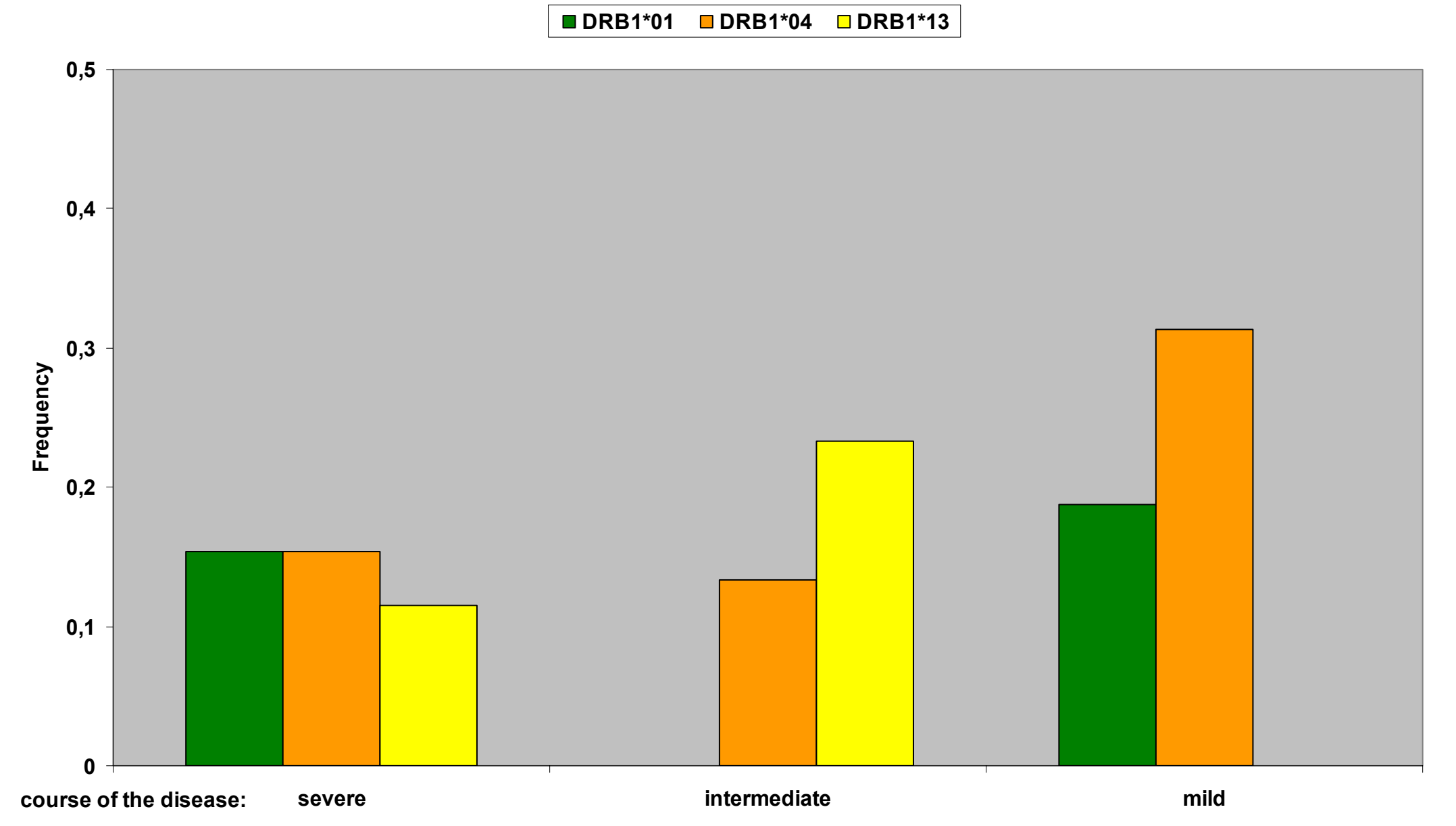
(Freiberger et al; Hum Immunol 2002)

GENOTYPE-PHENOTYPE RELATIONSHIP

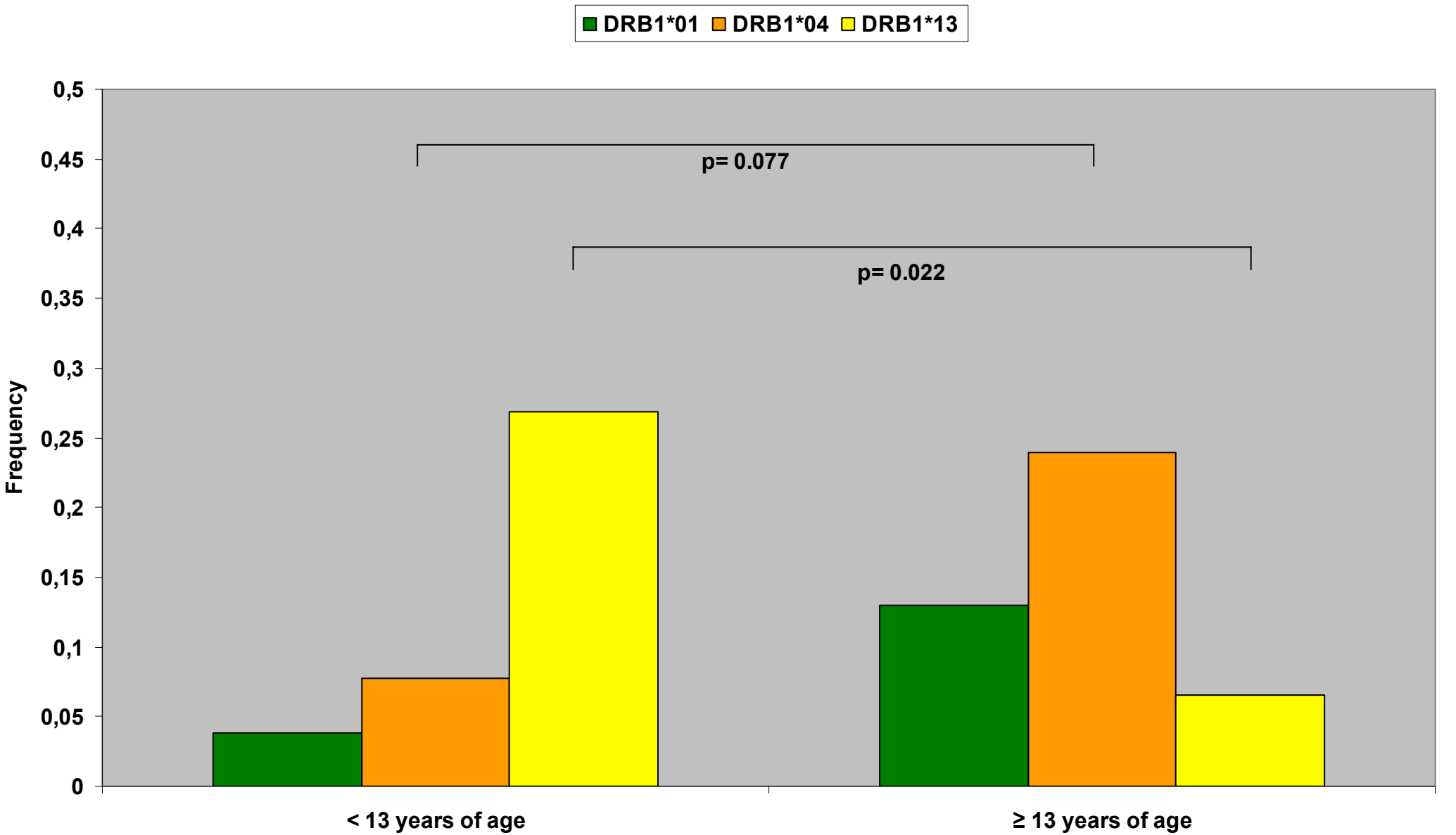
GENETIC FACTORS POTENTIALLY INFLUENCING CLINICAL MANIFESTATION OF HAE

- C1 INH gene
- BRADYKININ RECEPTOR gene
- HLA

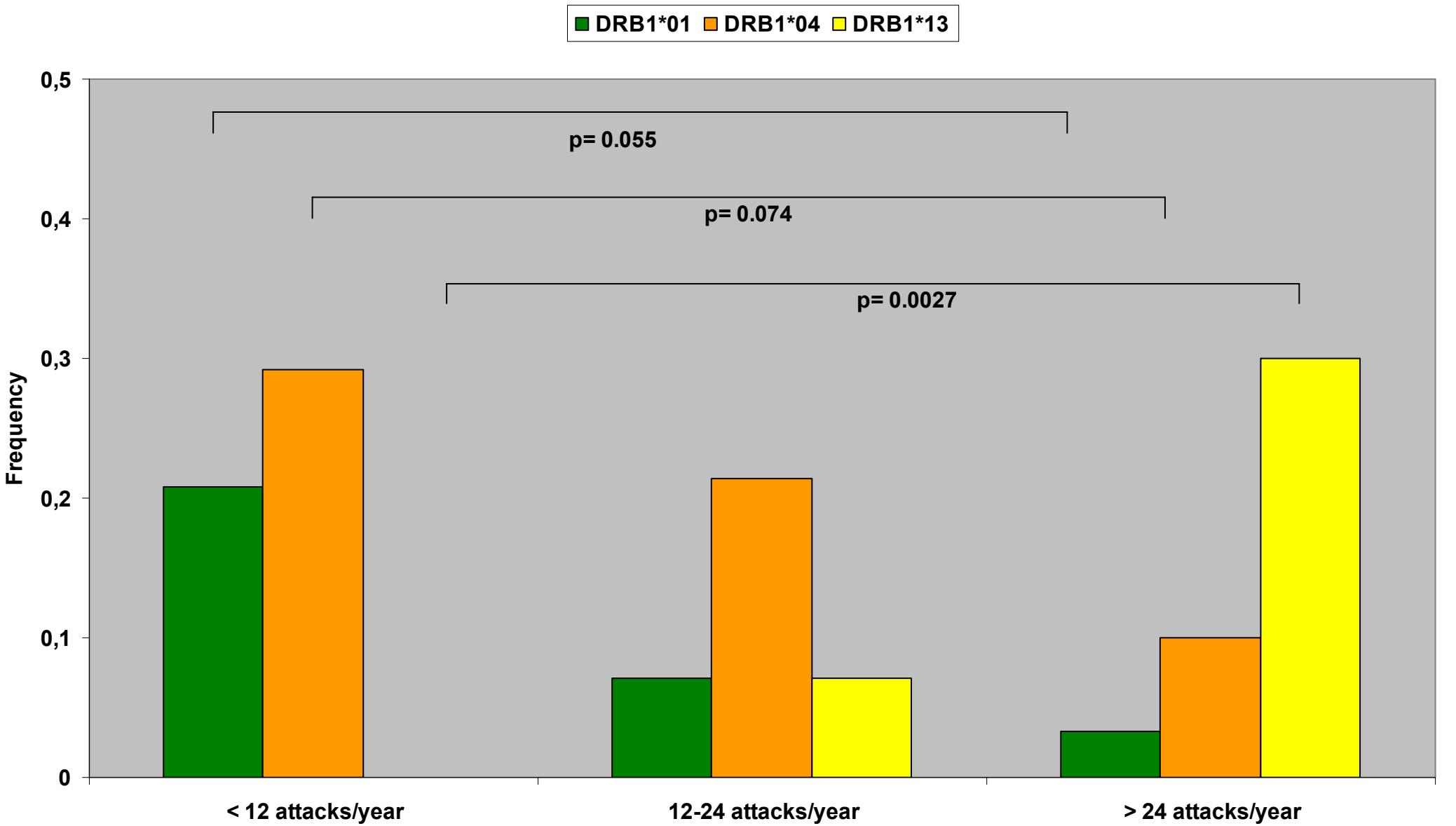
Frequency of HLA-DRB1*01, *04 and *13 alleles in HAE patients sorted according to the disease severity



Frequency of HLA-DRB1*01, *04 and *13 alleles in HAE patients sorted according to the onset of clinical symptoms



Frequency of HLA-DRB1*01, *04 and *13 alleles in HAE patients sorted according to the frequency of attacks



GENOTYPE-PHENOTYPE RELATIONSHIP

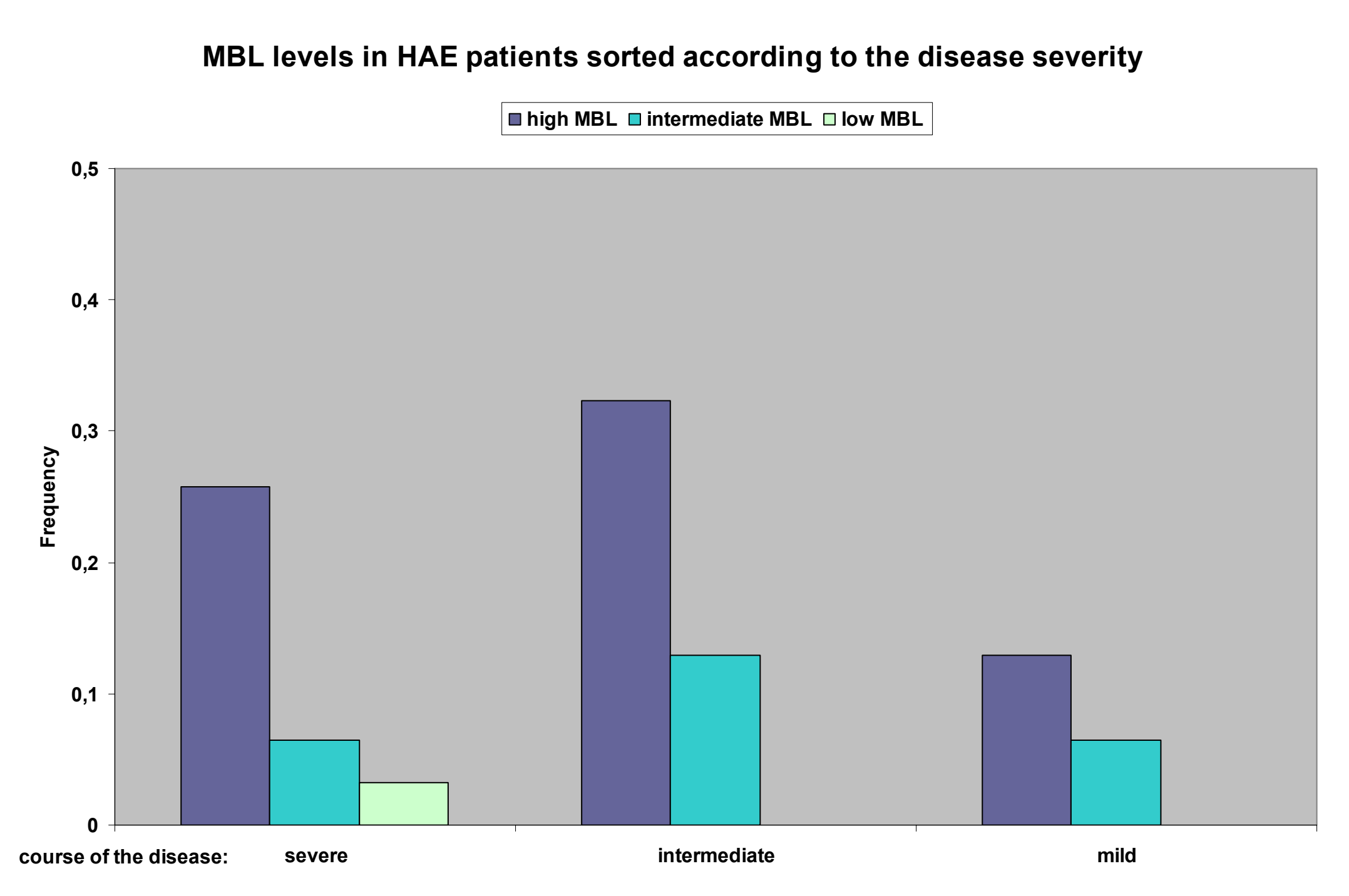
HLA

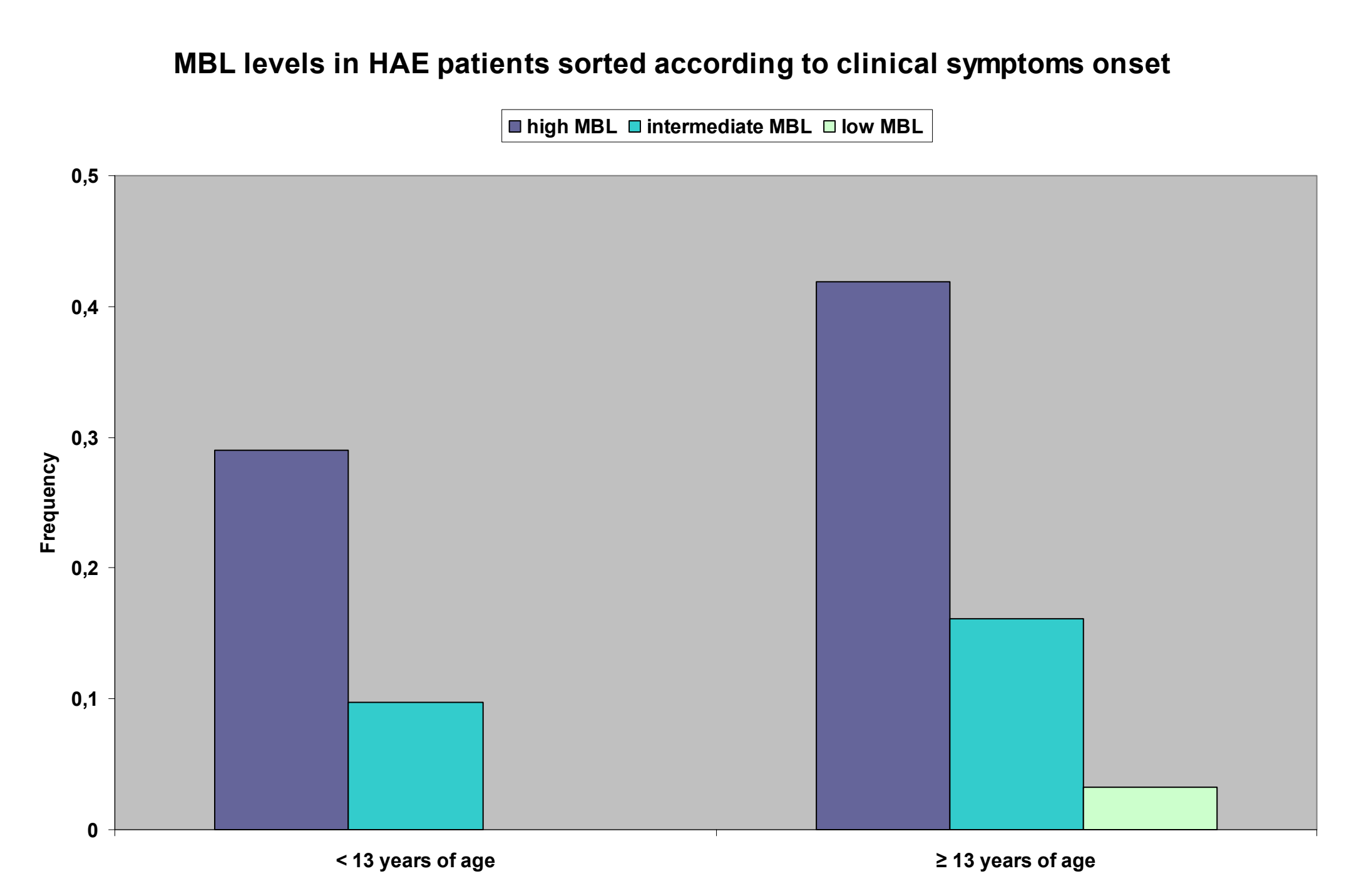
- certain HLA molecules may have a substantial modifying effect on HAE phenotype
- further analyses of the larger number of patients are required to confirm this hypothesis
- other genes being in a linkage disequilibrium with the MHC locus may play a role in clinical manifestation of HAE (C4?)

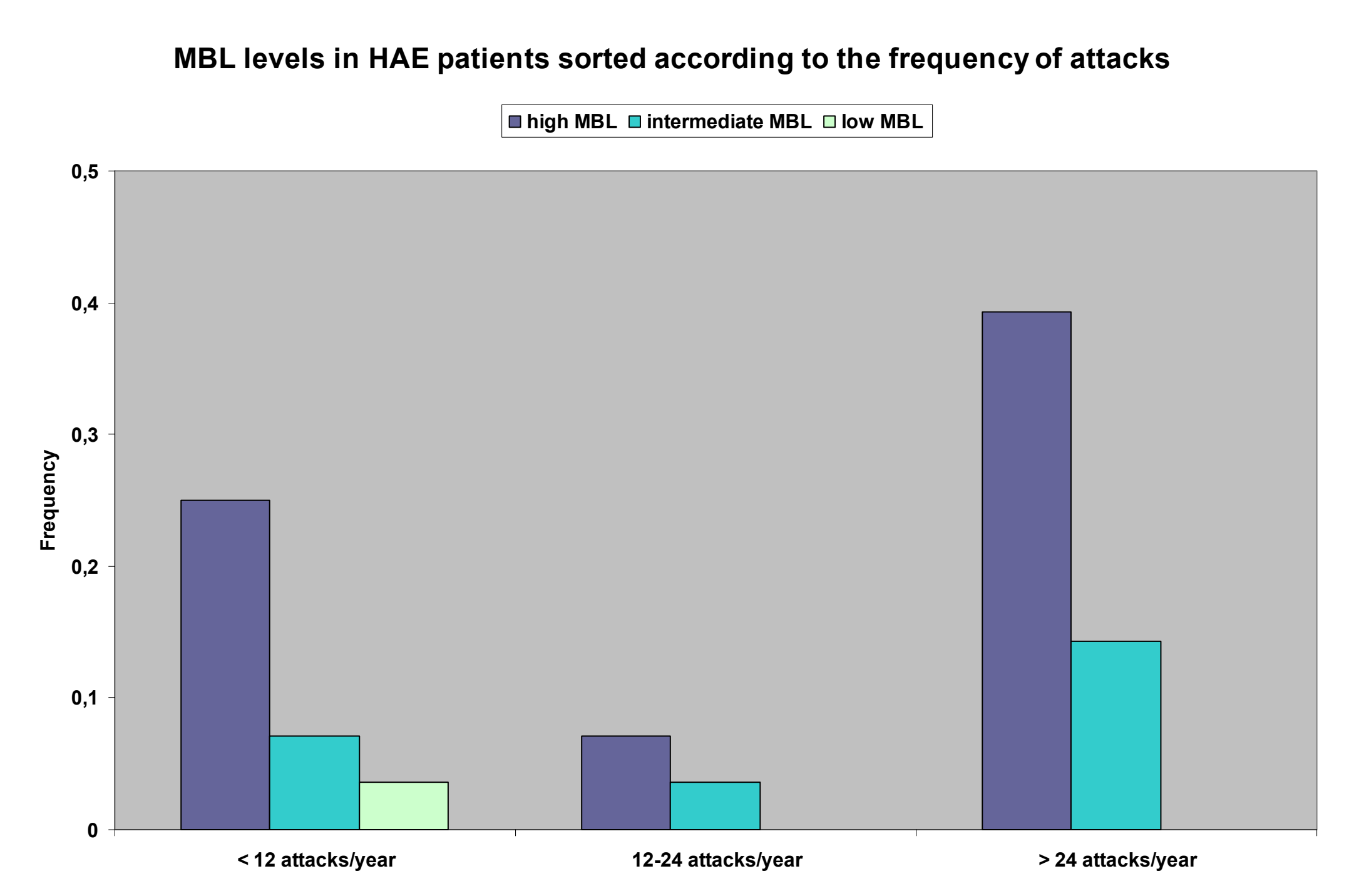
GENOTYPE-PHENOTYPE RELATIONSHIP

GENETIC FACTORS POTENTIALLY INFLUENCING CLINICAL MANIFESTATION OF HAE

- C1 INH gene
- BRADYKININ RECEPTOR gene
- HLA
- MBL
  - C1 INH blocks MASPs
  - speculation: alternative complement pathway activation is facilitated in C1 INH deficiency – increased susceptibility to edema formation; MBL def. could negatively influence edema formation


MBL levels in HAE patients sorted according to the disease severity
high MBL
intermediate MBL
low MBL
0,5
0,4
0,3
0,2
0,1
0
Frequency
course of the disease:
severe
intermediate
mild


MBL levels in HAE patients sorted according to clinical symptoms onset
high MBL
intermediate MBL
low MBL
0,5
0,4
0,3
0,2
0,1
0
Frequency
< 13 years of age
≥ 13 years of age


MBL levels in HAE patients sorted according to the frequency of attacks
high MBL
intermediate MBL
low MBL
Frequency
0,5
0,4
0,3
0,2
0,1
0
< 12 attacks/year
12-24 attacks/year
> 24 attacks/year

GENOTYPE-PHENOTYPE RELATIONSHIP

GENETIC FACTORS POTENTIALLY INFLUENCING CLINICAL MANIFESTATION OF HAE

- C1 INH gene
- BRADYKININ RECEPTOR gene
- MBL
- HLA
- ACE
  - deletion/insertion polymorphism in the ACE gene modulates bradykinine metabolism in vivo in human
- other genes

ACKNOWLEDGEMENTS

Hana Grombiříková MSc.

Lucie Kopálková Bc.

Martina Vyskočilová Bc., Věra Karpíšková

Prof. Jiří Litzman MD, PhD

Pavel Kuklínek, MD, PhD

…