Association of respiratory pathology and genetic polymorphism of the Vitamin D receptor

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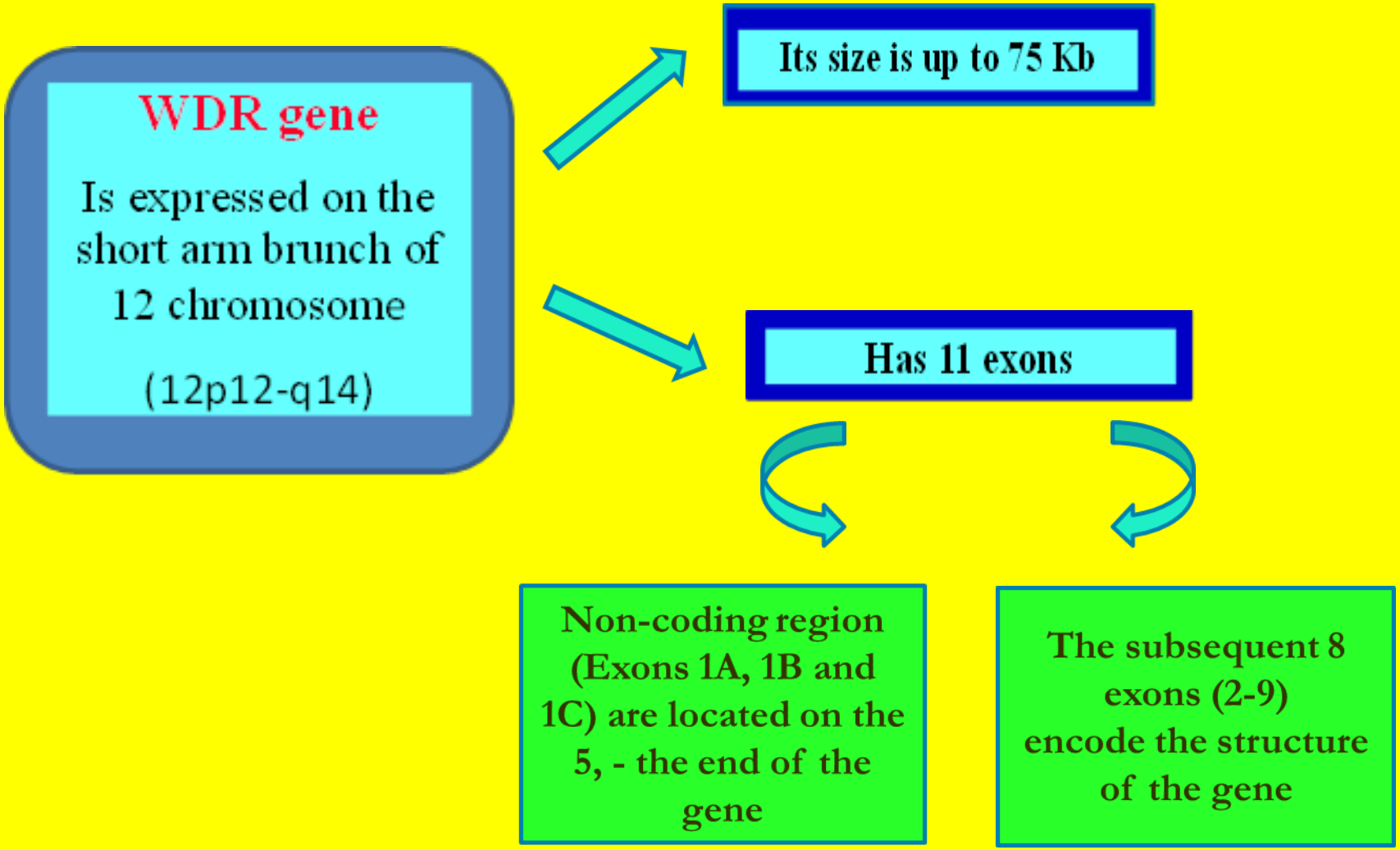
Introduction

The views of scientists on the **role of VitD** deficiency in the development of **obstructive pulmonary pathology** are completely different: some argue that this is **a key factor in the global asthma epidemic**, while others argue the negative effect of high doses of VitD in broncho-obstruction [G. Utz, A. M. Hauk, 1976] .

The aim of work

was to analyze the literature data about the genetic polymorphism of the VitD receptor in association with respiratory pathology.

STRUCTURE OF THE VDR RECEPTOR



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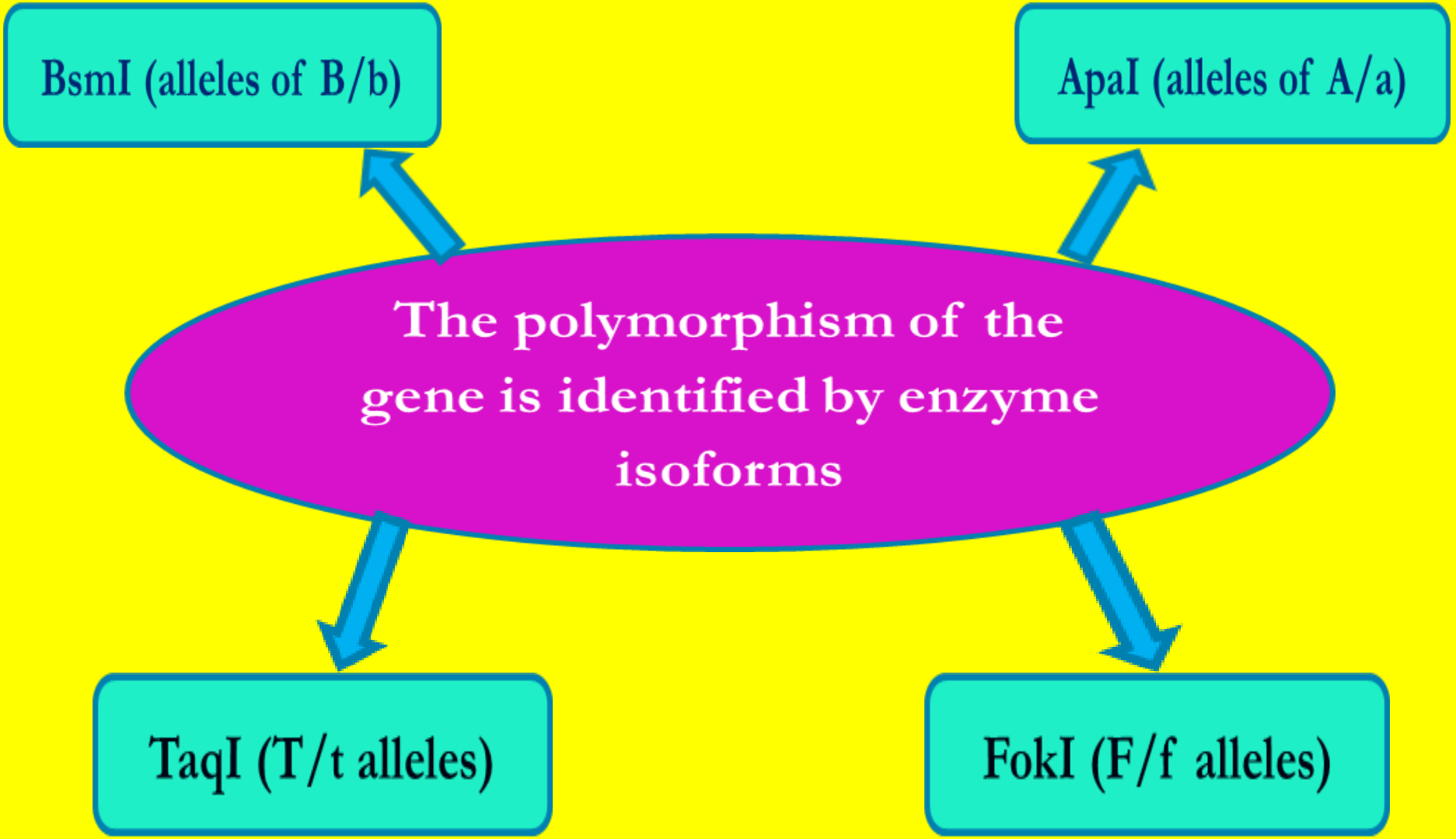

STRUCTURE OF THE VDR

Russia

Putilin and al. (St. Petersburg, Moscow, 2006):

- **TT genotype VDR** in females with ASTHMA associated with normal BONE MINERALE TISSUE (minimum fractures in anamnesis);
- **Tt genotype VDR** was characterized by osteopenia and more cases of fractures, than in previous genotype;
- **Genotype of tt-alleles** was described as osteoporosis with a maximum cases of fractures of the axial and peripheral skeleton;
- **TT-allele** indicates the absence of a restriction site for TaqI endonuclease.

AGE AND VDR POLYMORPHISM

Beirut, USA

Arabi A. at al. (2010):

- polymorphism of VDR was associated with restriction enzymes Bsml, TaqI, and ApaI;
- These variants of heterozygous genotypes were found in different age groups (young – 10-17 years and elderly – 65-85 years);
- **no differences in the genotype frequency by gender**, as was the distribution of VDR genotypes among young and elderly, heterozygous boys had lower levels of parathyroid hormone (PTH), with a similar tendency in older women;
- heterozygous elderly women had a higher bone density. **Obviously, the relationship between the polymorphism of VDR and BMT varies depending on age or gender.**

AGE AND VDR POLYMORPHISM

Great Britain

In the National Institute of Health (London), was studied the genetic mechanisms of vitamin D in the muscles.

- The level of calcitriol and parathyroid hormone was significantly lower in COPD. With the help of muscle biopsy (with the evaluation by PCR of heavy chains of muscle myosin, with variants of MHCI, IIa, IIx), it was established that in COPD, in comparison with the control group, the level of MHCI (but not MHCII or MHCIIx) is significantly lower, although the mRNA content Myogenic regulatory factor (MRF) did not differ in groups.

- The authors took into account the atrophy of the muscles, the severity of the disease, the frequency of exacerbations - but no connections were found. **Hypothesize: the results suggest that there is resistance to vitamin D in COPD** [A. S. Jackson, D. Shrikrishna, J. Kelly [et al.] , 2013].

VDR POLYMORPHISM IN DIFFERENT POPULATIONS

Japan

In 1997 Arai H. et al. investigated the frequency of VDR alleles among Japanese women (24-70 years), and the BMD in 110 healthy premenopausal women (24-45 years) with an evaluation of the polymorphism of the VDR.

Results: in **13.4%** of women – **MM**; **31.4% - mm**, and **55.2% - Mm**, regardless of age. BMT of the lumbar division in both groups was significantly higher in the VDR genotype in homozygotes mm.

Obviously, different alleles cause differences in the absorption of calcium.

VDR POLYMORPHISM IN DIFFERENT POPULATIONS

India

The variants of the genotype for FokI and TaqI polymorphisms were determined: FF 59%, Ff 36%, ff 5%, for TT 49%, Tt 43% and tt 8%, respectively,

in men - more often FF-variant (64% versus 52.5% of women) and TT (51% versus 45%), which reflects the possibility of differences not only in populations but also among the inhabitants of India.

VDR POLYMORPHISM IN DIFFERENT POPULATIONS

Significant differences for strong correlation with vitamin D occurred only for TaqI SNP In 34 out of 100 people, low levels of vitamin D were found. These data differed even from FokI and TaqI polymorphisms: FF - 44%, Ff - 49%, ff - 7%,
for TT - 49%, Tt - 40% and tt - 11%, respectively, confirmed for the population of Northern India

[A.A. Bhanushali, N. Lajpal, S.S. Kulkarni [et al.], 2009].

VITAMIN D AND GCS

- The relationship between vitamin D and glucocorticosteroids (GCS) regulation is variable.
- Practically safe doses of GCS do not exist, even in the treatment of obstructive syndromes by inhaled GCS [A.M. Путилин, М.В. Москаленко, И.А. Баранова [и др.] , 2006; Royal College of Physicians of London., 2002.].
- There is a hypothesis that GCS and vitamin D have a synergistic effect in asthma, especially in children [P. Majak, B. Rychlik, I. Stelmach, 2009; E. Goleva, D.A. Searing, L.P. Jackson [et al.] , 2012; E.R. Sutherland, E. Govela, L.P. Jackson [et al.], 2010; D.A. Searing, Y. Zhang, J.R. Murphy [et al.], 2010].
- Vitamin deficiency is associated with the need to increase doses of GCS therapy in asthma [D.A. Searing, Y. Zhang, J.R. Murphy [et al.], 2010].

Experimental studies

USA, Japan

The **lack of VDR** in mice caused early development of COPD and emphysema, chronic inflammation and immune dysregulation;

The **lack of VDR** in mice caused a reduction of 20% of all myofibrils as well as restriction of growth and differentiation of myocytes [A. Wittke, V. Weaver, B. D. Mahon [et al.], 2004; I. Endo, D. Inoue, T. Mitsui [et al.], 2003].

Potential mechanisms of VitD resistance may depend on cytochrome CYP27B1 (1α-hydroxylase), which converts calcidiol to calcitriol, to communicate with VDR in target organs.

The inhibition of the activity or expression of CYP27B1 will result in resistance to vitamin D, since VDR is widely present in the cytoplasm and determines non-genomic effects.

Conclusions

- The evaluation of VDR polymorphism as a risk factor of the vitamin D ineffectiveness depends not only on its concentration.

- Efficacy of therapy bronchial diseases can be determined by the VDR.

- From the presented studies, the dependence of VDR polymorphism from the geographic location, age and sex, the type of disease and the response to treatment by VitD is traced.


Thank you for attention!