The R156H variation in IL-12Rβ1 is not a mutation

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Abstract

Palamaro et al. describe a child with recurrent bronchopneumonia and very high IgE levels in which a variation, R156H, was found in the IL12RB1 gene that encodes the IL-12Rβ1 chain. Based on the absence of this variation in 50 unrelated individuals they conclude it is a mutation. We (van de Vosse and van Dissel) feel there is no reason to suspect a defect in IL-12 signaling based on the clinical data, nor evidence for a functional defect in IL-12 signaling in this patient. In addition, the variation is not novel and known as a polymorphism. Without any functional evidence that R156H is a mutation, the current claim is not substantiated.

Palamaro et al. respond to argue that the amino acid substitution, R156H described in the described case exerts a summatory effect, as a genetic cofactor, along with an additional and still unidentified molecular alteration of the same pathway.

Keywords: IL12RB1, IL-12Rβ1, Immunodeficiency, Mutation, Mycobacterial disease
of variations is, as a rule, counted from the first A of the ATG translation initiation codon, thus designating the variation found in this child as 467G>A [5]. We have analyzed R156H, as well as several other amino acid variations in IL-12Rβ1, in a retroviral expression system and found the R156H variation to be expressed on the cell membrane and not to have any effect on IL-12 responses as determined by measuring IFN-γ and IL-10 production, thus concluding R156H is most likely a harmless polymorphism [6].

Regardless of the literature provided here, one can analyze novel variations with the prediction programs SIFT (sift.jcvi.org/) and Polyphen (genetics.bwh.harvard.edu/phyh2/) to determine whether the substitution is more likely to be a mutation or a polymorphism. According to SIFT, which predicts the effect of amino acid substitutions on the basis of evolutionary conservation, the R156H variation is tolerated. According to Polyphen, predicting the possible impact of an amino acid substitution on the structure and function of a human protein using straightforward physical and comparative considerations, the R156H variation is benign. In order to, in the future, facilitate finding out whether a variation is already known to be a mutation, a polymorphism or a variation with an unknown effect, a database specific for IL12RB1 variations was recently launched at: www.LOVD.nl/IL12RB1.

In conclusion, we feel there is no reason to suspect a defect in IL-12 signaling based on the clinical data, nor evidence for a functional defect in IL-12 signaling in this patient. In addition, the variation identified is, based on various data sources, understood to be a polymorphism. Without any functional evidence that R156H is a mutation, the current claim is not substantiated.

Reply - Loredana Palamaro, Giuliana Giardino, Francesca Santamaria, Rosa Romano, Anna Fusco, Silvia Montella, Mariacarolina Salerno, Matilde Valeria Ursini and Claudio Pignata

Dear Editor,

In their comment to our case report on a child with interleukin 12 receptor alteration, van de Vosse and van Dissel raised the important issue of defining the causal relationship between a genetic variation and the phenotypic expression of a clinical entity, stating that the R156H in IL-12 beta1 receptor chain, reported in the patient described, is not a mutation but a variation also present in otherwise healthy individuals.

In principle, we agree with the Authors, in that to define the R156H allele as causative of the disease may be considered an overstatement. However, it should be emphasized that from recent whole genome sequencing studies, the analysis of the association between genetic variants and complex traits is establishing as a powerful strategy to assign a role also to variations otherwise considered polymorphisms. There are additional examples of genetic alterations, referred as polymorphisms and, therefore, with a prevalence in the general population higher than 1%, which are now considered important genetic susceptibility factors. The Ala91Val variation of the perforin gene is present in healthy controls, but is considered an important genetic element to confer susceptibility to lymphohistiocytosis [7–9].

In our case report we used the potent mitogen stimulation, which is widely recognized as a trigger of a Th1 polarization, to document the absence of the expression of the high affinity IL-12 R, consisting of both beta 1 and beta 2 chains. Certainly, a functional evidence of impaired IL-12 signaling could help to clarify the relationship between the genetic variation and the clinical phenotype. Unfortunately, this information is not available at moment.

As for the molecular analysis, this was performed on cDNA starting to count from the +1 site. However, this different enumeration does not interfere with the aminoacid substitution, which remains the same as before (R156H). The important finding of van de Vosse that this substitution doesn’t affect IL-12 R signaling would suggest that this variation in our case exerts a summatory effect, as a genetic cofactor, along with an additional and still unidentified molecular alteration of the same pathway.

Competing interests
The authors declare that they have no competing interests.

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References
1. Palamaro L, Giardino G, Santamaria F, Romano R, Fusco A, Montella S, Salerno M, Ursini MV, Pignata C: Interleukin 12 receptor deficiency in a child with recurrent bronchopneumonia and very high IgE levels. Ital J Pediatr 2012, 38:46.
2. van de Vosse E, Hoeve MA, Ottenhoff TH: Human genetics of intracellular infectious diseases: molecular and cellular immunity against mycobacteria and salmonellae. Lancet Infect Dis 2004, 4:739–749.
3. Arend SM, Cerda De Palou E, De Haas P, Janssen R, Hoeve MA, Verhard E, Ottenhoff TH, Van Soolingen D, Van Dissel JT: Pneumonia caused by Mycobacterium kansasi in a series of patients without recognized immune defect. Clin Microbiol Infect 2004, 10:738–744.
4. NCBi SNP database, build 133, released November 2011, http://www.ncbi.nlm.nih.gov/snp/.
5. den Dunnen JT, Antonarakis SE: Nomenclature for the description of human sequence variations. Hum Genet 2001, 109:121–124.
6. van de Vosse E, de Paus RA, van Dissel JT, Ottenhoff TH: Molecular complementation of IL-12Rβ1 deficiency reveals functional differences
between IL-12Rβ1 alleles including partial IL-12Rβ1 deficiency. Hum Mol Genet 2005, 14:3847–3855.

7. Busiello R, Fimiani G, Miano G, Aricò M, Sanròo A, Ursini MV, Pignata C: A91V perforin variation in healthy subjects and FHLH patients. Int J Immunogenet 2006, 33:123–125.

8. Busiello R, Adriani M, Locatelli F, Galgani M, Fimiani G, Clementi R, Ursini MV, Racioppi L, Pignata C: Atypical features of familial hemophagocytic lymphohistiocytosis. Blood 2004, 103:4610–4612.

9. Zhang K, Jordan MB, Marsh RA, Johnson JA, Kissell D, Meller J, Villanueva J, Risma KA, Wei Q, Klein PS, Filipovich AH: Hypomorphic mutations in PRF1, MUNC13-4, and STXBP2 are associated with adult-onset familial HLH. Blood 2011, 118:5794–5798.

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