

EDITORIAL

Clinical and Experimental Allergy

Genetic variation in the beta subunit of the high affinity IgE receptor and atopy and asthma

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This issue features two articles providing further evidence that genetic variants of the beta subunit of the high affinity IgE (FcεRI-β) – and in particular a gene promoter variant, substituting T for C nucleotide at position -109 – may contribute to the development or expression of asthma.

Kim et al. from Korea [1] report that T -109 up-regulates beta function through enhanced gene promoter activity, as determined by transfection experiments in cell lines. T -109 also associates with the presence of high IgE to staphylococcal enterotoxin in aspirin sensitive asthmatics. The group consider that the variant may hence augment the expression of asthma through increased beta expression on pulmonary mast cells holding IgE to staphylococcal enterotoxin.

Hizawa et al. from Japan [2] report that T -109 (and also CC -654 in haplotype analysis) associate with less asthma. In the same study they show that the 5G allele of plasma activator inhibitor 1 (PAI-1) associates with less asthma, and that the variants at both loci may interact in their effects on the risk of asthma. The group consider that the functional impact of variants of FcεRI-β remain difficult to pin down because of the co-inheritance of different variants spanning the whole gene. Their observations of the 5G/4G variant of PAI-1 build on previous observations that this functional variant (4G shows enhanced transcription and hence up-regulated function in comparison with 5G) impacts on inhibition of fibrinolysis and hence remodeling of the bronchus after mast cell driven inflammation.

Unraveling the genetics of common diseases holds great promise for improved prevention and treatments in the future [3]; but the challenge in this unraveling has been

and continues to be serious. This derives from the heterogeneous molecular pathology that comes from lumping clinical cases under one banner such as “asthma”. This is in turn a reflection of the reality that the genetic risks for the common diseases reside very largely in common genetic variants, each promoting moderate rather than major functional effect. Clinical disease ensues when individuals hold disease-promoting variants at a number of loci (polygenic disorder); moreover the combination of variants held at different loci in different individuals with same clinical disease will vary (genetic heterogeneity).

The study of the molecular genetics of both asthma and atopic allergy exemplifies these complexities well. Multiple chromosomal regions of genetic linkage have been observed. Some are related principally to asthma, others to atopy. Some of the specific loci implicated, such as those that impact on Th-2 signalling [4,5], are readily understandable in molecular pathological terms—others such as ADAM33, PHF11 and GPRA [6] are the subject of productive on-going investigation. Very many linkages and associations have been replicated in some way and in some populations—but instances of variable results across case series and ethnic groups abound. Polygenic effects are important, where a number of common variants at different loci interact with the environment to result in clinical phenotypes. Hence odds ratios for combined genotypes are substantially greater than ORs for single loci, eg odds ratios for combined genotypes at IL-13, IL4Ra and STAT-6 in Th-2 signalling [5]. In some instances, there may be the first glimpses of the evolutionary origin of these asthma and atopy promoting variants, for example in their possible protection against parasitic worm infections [7,8].

What then specifically of the role of genetic variants FcεRI-β in asthma and atopy? The reports of Kim et al and Hizawa et al. support a significant role for the gene—but together re-emphasise unraveled complexities at the locus. FcεRI-β—through chromosome 11q13 – was the first non-HLA locus linked to asthma and atopy [9,10]. Despite early non-replications it's evident now that genetic

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linkage, in family studies, to chromosomal region 11q13 is replicable across different populations. Mapping of the region, allowing for the difficulties of heterogeneity, strongly favour FcεRI-β as the locus at that site [11]. Association studies across different populations are also reproducible [1,2].

But attempts to gain final proof of the involvement of beta variants in promoting asthma and atopy—through the demonstration of functional change—have not so far succeeded. These attempts have helped unearth remarkable complexities in the intrinsic actions of FcεRI-β itself and—complexities that have probably so far undermined the attempts to understand how genetic variants of FcεRI-β change function. But that may be about to change.

Beta is one of the sub-units of the high affinity IgE receptor—together with the alpha and gamma subunits [12]. The importance of IgE based mechanisms in asthma as been re-emphasized by the therapeutic impact of humanized anti-IgE monoclonal antibody treatment for atopic asthma [13]. FcεRI-β contributes to the receptor on mast cells in an α -β-γ² configuration, but is absent from the receptor as expressed on antigen presenting cells where the configuration is α -γ² [14,15].

When FcεRI-β is present on mast cell bound high affinity IgE receptor, it appears not to contribute to either IgE binding or receptor signaling—which are respectively conferred by the alpha and gamma subunits [15,16]. Instead, recent experiments indicate an amplifier function for beta [17]. Firstly, beta acts as an amplifier of signaling through the α -β-γ² receptor itself [18]. More intriguingly, beta plays a key role in amplifying the necessary processing through glycosylation of alpha subunit protein at the cellular endoplasmic reticulum, and the delivery of alpha to the surface of the mast cell [19]. These amplifier actions of beta are hence vital to allergen-IgE mediated degranulation of mast cells in the bronchial epithelium. The action of the molecule as an amplifying element suggests that subtle changes in the relative level of FcεRI-β expression may impact on mast cell triggering.

This amplifier role of beta protein is further complicated by the natural expression of FcεRI-β protein both as a full length protein and as a truncated protein. The truncated protein lacks the normal 4th trans-membrane domain—which is due to natural alternative splicing of beta RNA in which there is inclusion of intron 5, and which introduces a stop codon. Moreover full beta and truncated beta have opposing functions—full beta accounts for the amplifying functions referred to, whereas truncated beta is inhibitory to alpha processing and delivery to the mast cell surface [20].

It's perhaps notable that the common I181L-I183V variant of beta—and which was first associated with asthma and atopy—is within the 4th trans-membrane domain which is deleted through alternative gene splicing. It's possible that the function-modulating actions of this

variant pertain strictly to influencing beta amplifying actions as described—and this now requires thoughtful testing. With regards to other variants, this issue's publication by Kim et al. suggest that the promoter variant -109 T/C may influence beta promoter activity and could hence quantitatively regulate the production of beta protein. This now needs further testing.

In conclusion, the story of beta variants in asthma and atopy continues to run—and at last we seem a little closer to properly understanding these complex effects.

References

- Kim S-H, Bae J-S, Holloway JW, Lee J-T, Suh C-H, Nahm D-H, Park H-S. Polymorphism of MS4A2 (-109T > C) encoding beta chain of high affinity IgE receptor is associated with susceptibility to aspirin-intolerant asthma. *Clin Exp Allergy* 2006; 36:877–83.
- Hizawa N, Maeda Y, Konno S, Fukui Y, Takahashi D, Nishimura M. Genetic polymorphisms at FcεRIβ and PAI-1 and asthma susceptibility. *Clin Exp Allergy* 2006; 36:872–6.
- Cookson W, Moffatt M. Making sense of asthma genes. *N Engl J Med* 2004; 351:1794–6.
- Gao PS, Heller NM, Walker W, Chen CH, Moller M, Plunkett B, Roberts MH, Schleimer RP, Hopkin JM, Huang SK. Variation in dinucleotide (GT) repeat sequence in the first exon of the STAT6 gene is associated with atopic asthma and differentially regulates the promoter activity in vitro. *J Med Genet* 2004; 41:535–9.
- Kabesch M, Schedel M, Carr D, Woitsch B, Fritzsche C, Weiland SK, von Mutius E. IL-4/IL-13 pathway genetics strongly influence serum IgE levels and childhood asthma. *J Allergy Clin Immunol* 2006; 117:269–74.
- Allen M, Heinzmann A, Noguchi E, Abecasis G, Broxholme J, Ponting CP, Bhattacharyya S, Tinsley J, Zhang Y, Holt R, Jones EY, Lench N, Carey A, Jones H, Dickens NJ, Dimon C, Nicholls R, Baker C, Xue L, Townsend E, Kabesch M, Weiland SK, Carr D, von Mutius E, Adcock IM, Barnes PJ, Lathrop GM, Edwards M, Moffatt MF, Cookson WO. Positional cloning of a novel gene influencing asthma from chromosome 2q14. *Nat Genet* 2003; 35:258–63.
- Peisong G, Yamasaki A, Mao XQ, Enomoto T, Feng Z, Gloria-Bottini F, Bottini E, Shirakawa T, Sun D, Hopkin JM. An asthma-associated genetic variant of STAT6 predicts low burden of ascaris worm infestation. *Genes Immun* 2004; 5:58–62.
- Palmer LJ, Pare PD, Faux JA, Moffatt MF, Daniels SE, LeSouef PN, Bremner PR, Mockford E, Gracey M, Spargo R, Musk AW, Cookson WO. Fc epsilon R1-beta polymorphism and total serum IgE levels in endemically parasitized Australian aborigines. *Am J Hum Genet* 1997; 61:182–8.
- Young RP, Sharp PA, Lynch JR, Faux JA, Lathrop GM, Cookson WO, Hopkin JM. Confirmation of genetic linkage between atopic IgE responses and chromosome 11q13. *J Med Genet* 1992; 29:236–8.
- Shirakawa T, Li A, Dubowitz M, Dekker JW, Shaw AE, Faux JA, Ra C, Cookson WO, Hopkin JM. Association between atopy and variants of the beta subunit of the high-affinity immunoglobulin E receptor. *Nat Genet* 1994; 7:125–9.
- Traherne JA, Hill MR, Hysi P, D'Amato M, Broxholme J, Mott R, Moffatt MF, Cookson WO. LD mapping of maternally and non-

- maternally derived alleles and atopy in FcepsilonRI-beta. *Hum Mol Genet* 2003; 12:2577-85.
- 12 Kinet JP. The high-affinity IgE receptor (Fc epsilon RI): from physiology to pathology. *Annu Rev Immunol* 1999; 17: 931-72.
- 13 Marcus P. Practice Management Committee, American College of Chest Physicians. Incorporating anti-IgE (omalizumab) therapy into pulmonary medicine practice: practice management implications. *Chest* 2006; 129:466-74.
- 14 Nadler MJ, Matthews SA, Turner H, Kinet JP. Signal transduction by the high-affinity immunoglobulin E receptor Fc epsilon. *Adv Immunol* 2000; 76:325-55.
- 15 Kraft S, Rana S, Jouvin MH, Kinet JP. The role of the FcepsilonRI beta-chain in allergic diseases. *Int Arch Allergy Immunol* 2004; 135:62-72.
- 16 Blank U, Jouvin MH, Guerin-Marchand C, Kinet JP. The high-affinity IgE receptor: lessons from structural analysis. *Med Sci (Paris)* 2003; 19:63-9.
- 17 Scharenberg AM, Kinet JP. Fc epsilon RI and the FcR-beta amplifier. *Int Arch Allergy Immunol* 1997; 113 (1-3):42-4.
- 18 Dombrowicz D, Lin S, Flamand V, Brini AT, Koller BH, Kinet JP. Allergy-associated FcRbeta is a molecular amplifier of IgE- and IgG-mediated in vivo responses. *Immunity* 1998; 8:517-29.
- 19 Fiebiger E, Tortorella D, Jouvin MH, Kinet JP, Ploegh HL. Cotranslational endoplasmic reticulum assembly of Fc{varepsilon}RI controls the formation of functional IgE-binding receptors. *J Exp Med* 2005; 201:267-77.
- 20 Donnadieu E, Jouvin MH, Kinet JP. A second amplifier function for the allergy-associated Fc(epsilon)RI-beta subunit. *Immunity* 2000; 12:515-23.