

EDITORIAL

Maternal inheritance of atopy?

Although it is clear that the offspring of atopic parents are at increased risk of developing atopy [1], debate persists over the pattern of inheritance [2]. Among the more intriguing possibilities is preferential inheritance through the maternal line, and Johnson *et al.* provide further evidence in this edition of *Clinical and Experimental Allergy* [3]. Although there is the possibility for such an effect at the molecular level [4], the evidence remains conflicting [5–16].

Although an increased risk of atopic inheritance through the mother was first described by Bray in 1931 [5], it was over 50 years later that 1982 Happle and Schnyder [6] reported that the proportion of atopic children was considerably higher if the mother was atopic (48%) than if the father was atopic (33%). They interpreted this as evidence for the 'Carter effect' — that atopy is a polygenic disease and the more predisposing genes the individual possesses, the more likely they are to develop atopy. As the threshold for atopy is greater for females than in males, a female must possess more predisposing genes for disease expression. Consequently, the male offspring of atopic mothers will have higher rates of atopy.

Interpretation of those studies that have specifically addressed maternal inheritance is hampered by confounding factors. Foremost of these is the likelihood of recruitment bias in studies conducted through antenatal clinics with a likely excess of atopic mothers compared to fathers. Even random samples may be liable to this bias when mothers are the principal carers. Ascertainment of the father's atopic status through the mother such as employed by Johnson [2] is a further source of phenotypic uncertainty. Further factors to be considered in the interpretation of such studies include the means of atopic ascertainment (skin-prick tests, specific IgE or total IgE); the age dependent penetrance of atopy, with a discordance between peak age for skin-prick positivity and total serum IgE, and a higher rate of atopy in boys than girls [17].

Despite these concerns a number of investigators have reported preferential inheritance of atopy through the maternal line, albeit with differing atopic phenotypes. The most frequently reported association is between any maternal atopy or maternal serum total IgE and the child's total serum IgE [7–11]. For example, Magnuson [8] related cord serum IgE in 190 newborns to parental history of atopic disease. Using 1.2 IU/mL as the upper limit of normal for cord IgE, mothers with a history of atopic diseases had significantly greater number

offspring with high IgE (15 of 37) than did offspring of atopic fathers (one of 29). Significantly however, the risk of development of atopic disease by the age of 18 months was no higher if the mother or father was atopic. Similarly in a community study of 344 nuclear families, Lebowitz [7] reported that the relationship between a child's serum total IgE was closer to the mothers IgE than to the fathers. However, the presence of positive allergen skin-prick result in the child was influenced more by the fathers skin-prick test results than the mothers. Conversely, the risk of sensitization to four environmental allergens in over 300 German children [13] was greatest if the mother was also sensitized to the same allergen, but was also increased if mother was sensitized to one of the other allergens. The risk was not increased if father was sensitized to either the same allergen, or another allergen.

Likewise, the infants of atopic mothers are at significantly increased risk of atopic dermatitis in the first 2 years of life compared with the infants of atopic fathers [11,12]. In a prospective study of 39 atopic parents [12], where the other partner was non-atopic, the risk of atopic dermatitis in the child was significantly increased when the mother (nine of 19) was atopic compared with when the father (two of 20) was atopic.

Preferential maternal inheritance of atopy was not however, demonstrated in the largest study of over 6000 randomly selected children [14]. The risk of asthma was increased in those children whose parents had asthma, but not if their parents had atopic dermatitis or hay fever. The risk of hay fever was increased if the parents had asthma or atopic dermatitis but was greatest if the parent also had hay fever. Similarly the risk of atopic dermatitis was increased if the parent had asthma or rhinitis but was greatest if the parent had atopic dermatitis. The risk of development of atopic dermatitis and hay fever was similar for both maternal and paternal transmission, but the odds ratio for the child developing asthma was 4.4 (95% CI 2.5–7.8) if the father was asthmatic, while there was no increase in odds ratio if the mother was asthmatic.

The consideration of preferential inheritance of atopy through the mother was given new impetus by the findings of Cookson and Hopkin and their co-workers in Oxford. Using a broad definition of atopy (any one of) skin-prick weal of 2 mm or more than control; specific IgE and RAST score > 0.35 PRU/mL, raised total serum IgE corrected for (age), they identified a single major autosomal dominant atopy gene on chromosome

11q13 with strong evidence of linkage [18]. They supported this finding in 64 small nuclear families where again they found linkage for atopy to 11q13 [19]. Intriguingly, there was also a significant difference in θ between males and females, with estimated θ male = 0.182 and θ female = 0.001 ($\chi^2 = 6.44$, $P < 0.02$). Using affected sibling pair methods they then compared sharing of paternal and maternal alleles in all the 723 subjects that they had genotyped [20]. They found that 125 (62%) of affected sibling pairs shared their maternal allele and 78 (38%) did not – again a significant difference from the expected 50/50 ratio. There was no significant difference in the allele's that were paternal in origin. The significant sharing of maternal alleles in affected sibling pairs remained consistent if skin-test positivity alone, RAST positivity alone or on high total serum IgE alone was used for atopic definition.

The group in Oxford have since attributed their findings to a single base pair substitution of a leucine for an isoleucine residue at position 181 (Leu181) in the first of four transmembrane domains of the gene encoding the β subunit of $Fc\epsilon RI\beta$ located on chromosome 11q13 [4, 21]. In a sample of over 160 subjects unselected for atopy, the Leu181 variant was present in 15% of individuals, of whom 56% were atopic. Furthermore, amongst 60 unrelated atopic families, the Leu181 variant was identified in 10 (17%) families. In each family Leu181 was maternally inherited, and strongly associated with atopy. Of note is that only one subject had a 'double' mutation of leucine substitution at position 183 in addition to leucine at 181 (Leu181/Leu183). In a recent report from the same group of a random population in Busselton, Western Australia, 4% of cases tested positive for a Leu181/Leu183 variant, while no cases tested positive for the Leu181 variant [22]. All 13 children who inherited the Leu181/Leu183 variant maternally were atopic, while none of the eight children who inherited the variant paternally were atopic.

Other investigators have been unable to demonstrate differences in sharing of paternal and maternal alleles at 11q13 [15,16,23]. Furthermore there has been a striking inability for other investigators to replicate the $Fc\epsilon RI\beta$ findings. In an Australian twin study comprising over 900 individuals, Duffy *et al.* were unable to detect any individuals possessing either the Leu181, or the Leu181/Leu183 variants, despite the presence of successful positive controls [24]. There has been a similar inability to detect either variant in a Japanese population [25]. It is possible that the discrepancies are technical, the result of difficulties with the ARMS assay [26]. Nevertheless, the differences in allele frequency between Oxford and Busselton remain unexplained, and is of concern given that the genetic pools are likely to be of similar origin.

It is unlikely that either the Leu181 or the Leu181/Leu183 variants fully account for the reported linkage of atopy to 11q13. Given their dwindling reported frequency in random populations, they also seem unlikely to account for the reports of maternal inheritance of atopy. If so, what are the other putative mechanisms for maternal inheritance of atopy? Paternal genomic imprinting is the most widely considered possibility. Although genomic imprinting has been demonstrated on other chromosomes [27], there is no evidence for such an effect on chromosome 11q. Other possibilities include programming of the fetus *in utero* [28], either through changes in maternal nutrition during pregnancy, or through trans-placental passage of maternally derived cytokines. Supportive evidence for such effects is suggested by the observation that serum total IgE at 50 years of age is related to measurements at birth such as infant head circumference [28]. In the absence of stronger evidence, such suppositions are at present purely speculative.

What are we to make of these conflicting reports? Although there are a number of reports of higher cord total IgE in the newborn infants of atopic mothers [7–11], and that atopic dermatitis in the first year of life may be commoner in their offspring [11,12], concerns over selection bias must remain. There is no evidence for increased inheritance of atopic dermatitis through the maternal line in older children [14–16], and if anything evidence for increased inheritance of asthma through the paternal line [14]. Thus, preferential inheritance of atopy through the maternal line might only apply to cord IgE and atopic dermatitis in early life, and could reflect non-genetic factors such as programming of the fetus or trans-placental passage of maternally derived cytokines. It is difficult to interpret the significance of mutations in the $Fc\epsilon RI\beta$ without corroborating evidence from other investigators, and a clear explanation for discrepancies in allele frequencies.

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