Recurrence of acheiria in a second cousin: extremely large pedigrees may include ‘second cases’ by chance

Lamont and Salisbury report unilateral absence of the hand (acheiria) in an index case and in a second cousin. In their opinion the possibility that “both children could have been affected by chance . . . is too remote to be considered”. They found no common environmental factor, and proposed a “common mutant dominant gene”, transmitted from one of the shared grandparents, as “the most cogent explanation”. While not denying the logic of their suggestion, nor the evidence from recurrences of acheiria in sibs and in second and third degree relatives, as mentioned in their paper, we wish to point out that if one records pedigrees so as to include second cousins (fifth degree relatives) of the index case one is potentially including data on a very large number of persons indeed, and ‘recurrences’, on a chance basis, are not as unlikely as may initially appear to be the case.

Assuming a simple family structure of two children for every pair of parents (that is, a steady state, non-expanding population), and the recording, in the genetics clinic, of families to include only sibs, parents, grandparents, uncles/aunts, and first cousins of the index case, one would record data on $1 + 2 + 4 + 8 + 16 = 30$ other persons per family. Enlarging the pedigree to include second cousins, with the more recently born of their linking relatives, one would record four great uncles/aunts, eight first cousins once removed, and 16 second cousins, that is, a total of 41 relatives of the index case. Were one to include all first to fifth degree relatives in previous or contemporary generations (eight great grandparents, 16 great great grandparents, etc) one would obtain a total of 137 relatives per family, while still excluding generations younger than the index case.

Although we believe no families would possess information on all first to fifth degree relatives (that is, our estimate of 137 relatives is in that way unrealistic), our model of a family with only two children for each two parents underestimates family size. In our clinics we routinely record pedigrees to include grandparents, uncles/aunts, and first cousins, and examining the files of the first 25 families seen in Oxford in 1989 (referrals to a general genetics clinic) we found a total of 475 such relatives of the index cases, that is, an average of 19 per family (not 13, as would be expected on the ‘simple’ model). This suggests that our estimate of 41 relatives per family, if one extends to include second cousins, is also an underestimate. We found 4-68 uncles/aunts instead of the ‘expected’ two, and 7-32 first cousins instead of the ‘expected’ four, that is, each grandparental pair had on average 3-34 (4-68/2+1) offspring rather than two, and each of these persons had an average of 1-56 (7-32/4-68) live children at the time the pedigree was constructed. Assuming that fertility was no less in the previous (great grandparental) generation, we calculate an average of 9-36 great uncles/aunts, 31-26 first cousins once removed, and 48-89 second cousins, that is, a total of 108-51 relatives of the index case if families were to be recorded in this way (omitting all generations before the grandparental or after the index case).

Lamont and Salisbury give a birth prevalence for acheiria of 1 in 65 000. With about 600 000 live births in the UK per annum one would expect 92-3 births with acheiria within the last decade, and these would have a total of 10 015 relatives up to and including second cousins (92-3 x 108-51). The probability of acheiria, by chance, among these relatives would be 10 015/65 000 = 0-1541, and from the Poisson distribution the chance of one or more such families actually existing would be 14-28%.

However, Lamont and Salisbury quote an old reference for the birth prevalence of acheiria. From the Edinburgh Register of the Newborn, Rogala et al found birth prevalence of isolated transverse spinal absence defects to be 0-4 per 10 000, and this is in agreement with estimates one can make combining information from Birch-Jensen and from Wynne-Davies and Lamb. With this prevalence we would expect 240 UK cases in a decade, 26 042 extended family members, and a 64-7% chance of one or more families with recurrence on a chance basis. For all types of transverse forearm/hand defect the birth prevalence is much higher (5-8 per 10 000 from Wynne-Davies and Lamb), and one would expect 3480 UK cases within a decade, with 377 614 extended family; about 6% of these cases would be ‘familial’.

In conditions with a high birth prevalence the likelihood of chance recurrence within an extended family is considerable, and in general one should beware of arguing from such recurrences unless the necessary calculations have been made and a coincidence appears truly unlikely.

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This letter was shown to Drs Lamont and Salisbury, who reply as follows.

While not disputing the logic of this comment by Drs Lindenbaum and Firth on the possibility of recurrence of acheiria within families when considering the entire United Kingdom population, we would point out that our case report referred to one family with 10 relatives, other than the proband, descended from the common grandparents. For our quoted prevalence rate of acheiria of 1 in 65 000, the probability of recurrence would be 0-00015, surely a low figure. With the prevalence rate of 1 in 25 000 from the survey by Wynne-Davies and Lamb, the probability of recurrence in our family would be 0-0004. From a total of 2833 relatives, including those of third degree, of 102 probands with