Letters to the Editor

Interpreting the evidence for an association between the retinoic acid receptor locus and non-syndromic cleft lip with or without cleft palate

Vintiner et al recently reported the results of a negative association study for non-syndromic cleft lip with or without cleft palate (CL±P) and the Pax1 polymorphism at the retinoic acid receptor (RARA) locus, and concluded that their data failed to confirm the reported association between CL±P and RARA in Australian subjects.1 Failure to reject the null hypothesis in these data does not, however, constitute evidence against an association of the magnitude detected in the Australian study.2 The best estimate of the odds ratio (OR) for the association of CL±P and RARA in Australian subjects is 1-81 (table). The British data do not constitute evidence against such an association, since they provide relatively low power: 56% under a two sided alternative and 68% under a one sided alternative, to detect an odds ratio of this magnitude at α = 0.05. In fact, the direction of the association between the A2 allele and CL±P is consistent across studies, and the 95% confidence interval obtained in the British data includes the point estimate based on the Australian data (table). Moreover, tests of heterogeneity for the RARA allele frequencies were non-significant in both cases (p = 0.28) and controls (p = 0.96). Relative to the Australian data, the combined data provide slightly stronger evidence (p = 0.012) for a somewhat weaker association (OR = 1.60, 95% CI 1-10-2.30) between CL±P and the A2 allele of the RARA Pax1 polymorphism (table). Thus, while the British data are compatible with the null hypothesis, they are also consistent with the Australian data. Confirmation of an association between CL±P and RARA, therefore, awaits replication in study populations with sufficient power to detect an odds ratio of at least 1-60.

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Distribution of RARA allele frequencies

<table>
<thead>
<tr>
<th>Allele</th>
<th>A1</th>
<th>A2</th>
<th>A1</th>
<th>A2</th>
<th>Combined</th>
</tr>
</thead>
<tbody>
<tr>
<td>Controls</td>
<td>49</td>
<td>101</td>
<td>32</td>
<td>88</td>
<td>189</td>
</tr>
<tr>
<td>(p value)</td>
<td>0.621 (0.013)</td>
<td>0.955 (0.329)</td>
<td>0.624 (0.013)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>OR (95%CI)</td>
<td>1.81 (1.13-2.91)</td>
<td>1.34 (0.74-2.43)</td>
<td>1.60 (1.10-2.30)</td>
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</table>

* Excludes the single subject with an A3 allele.
† OR = bc/ad, 95% CI = exp [ln(OR)] ± 1.96 /a + b + 1/c + 1/d)0.5 where a and c refer to the number of A1 alleles in cases (that is, CL±P subjects) and controls, respectively, and b and d refer to the number of A2 alleles in cases and controls, respectively.

Letters of MII chromosome of the somes could have in inheritance in maternal in intentions in the mother. These results (figure). DXS255 48,XXXX,23 whereby maternal excessive MI and at heterozygosity and and were observed at one or all informative loci (data not shown).

Investigations of three 49,XXXXX cases (partial results of two have been published previously*) were similar to previous reports and showed that all four X chromosomes were maternal in origin with equal dosage of alleles at all heterozygous loci in the mother. These results support a mechanism of successive MI and MII meiotic non-disjunction in the mother involving both chromatid pairs in MII. This may also explain the inheritance in case 2, which, in addition, must have had a pre- or postfertilisation loss of the paternal sex chromosome. Case 3 could have originated either from a tetrasomy X oocyte with postmeiotic loss of one maternal chromosome or from successive MI and MII non-disjunctions with involvement of only one of the X chromatid pairs in MII (resulting in transmission of three X chromosomes to the oocyte).13

Case 1 of the present study, however, is the only case which cannot be explained by meiotic non-disjunction alone, since three copies of a single maternal X allele were observed for some loci. Therefore, either an extra X chromosome was present in the mother’s germ cells before meiosis, or the zygote originated from a 47,XXX karyotype, with the third maternal X duplicated in the zygote or early postzygotically. In either case, both meiotic and mitotic non-disjunctions would contribute to the X chromosome polyomy. Thus, although most cases of X chromosome tetrasomy are compatible with the hypothesis of successive meiotic non-disjunction in the mother, other mechanisms may also occasionally be involved.

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<td>172</td>
<td>26</td>
<td>96</td>
<td>72</td>
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