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Interrelationship of different dysraphic malformations and consequences for genetic counselling

SIR,

A girl in our paediatric care suffers from meningo-myelocele (lumbosacral) with peculiar additional features and an interesting family history. The pedigree suggested to us the possibility of a genetic relationship between different types of dysraphism (figure).

Our patient, apart from her spina bifida, has a very narrow arched palate impeding proper speech. Her articulation is almost as bad as if she had full cleft palate. Her otherwise healthy mother has the same anatomical and functional abnormality. The mother's brother had a defect of the abdominal wall and died in the neonatal period.

We wondered whether abdominal defects (omphalocele, gastroschisis) are relevant to familial disposition towards other closure defects (old term: status dysraphicus)?

We have not found clear indications of a causal relationship between failed closure of the neural tube and that of the ventral body wall. In one interesting family, however, three such defects were present together in one patient, while his three sibs had exomphalos only (one of them also had an arched palate and mandibular hypoplasia).

The distribution of dysraphic features in our family, too, raises the possibility of a common pathogenesis (be it genetic or environmental or both) of these malformations. If so the appearance of one of them would warrant measures to prevent, or to diagnose antenatally, the others. This conclusion is analogous to that drawn by Cohen and colleagues regarding preceding cases of hydrocephalus. Their argument was, of course, supported by a large number of relevant observations. I should be grateful for information on similar occurrences to the one I present in this letter.

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References


'Microcytogenetics' and Langer-Giedion syndrome

SIR,

The identification of minute cytogenetic aberrations in a few disorders of proved or suspected Mendelian origin is causing growing interest, and the term 'microcytogenetics' has been proposed by de Grouchy1 to denote this new field of research. Evidence is now available of associations such as aniridia–Wilms' tumour and 11p13 deletion, retinoblastoma and 13q14 deletion, Prader-Willi syndrome and chromosome 15, and X linked mental retardation and the Xq27→28 fragile site.

Recently Pfieffer2 and Bühler et al3 have suggested a new association between Langer-Giedion (LG) syndrome and small deletions of the long arm of chromosome 8. They have reported two patients, with del(8)(q13→q22) and del(8)(q24) respectively, showing the characteristic features of LG syndrome, including mental retardation, short stature, microcephaly, peculiar facies, cone-shaped epiphyses of the phalangeal and metacarpal bones, and multiple cartilaginous exostoses (MCE). Further evidence for a similar association has been provided by Fryns et al4 in a subject with a deletion of band 8q21. The patient displayed dysmorphic features reminiscent of LG syndrome and MCE, which were detected at 4 years, but were apparently absent at 15 months, when first examined.5

According to Bühler et al3 an association between
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two rare conditions such as 8q partial deletion and LG syndrome is too unlikely to result from chance. Therefore the possibility must be considered that LG syndrome results from a small chromosomal rearrangement. Alternatively, a Mendelian origin of LG syndrome can be reconciled with cytogenetic data only if due to "a recessive mutation which is unmasked by hemizygosity". 2

The clinical findings in three additional cases with 8q partial deletion, 4-8 involving bands 8q24.2, 8q21.3→24.3, and 8q13→22 respectively, do not provide further data to confirm the association hypothesis. All three patients showed some of the non-specific features of the LG syndrome, such as hypertelorism, bulbous nose, large protruding ears, and micrognathia, but none of them was reported to have MCE. The lack of the exostotic component of the syndrome could result from the very young age of the subjects (less than one year). Variable penetrance of MCE is suggested by Fryns et al. 4 and would be consistent with the older ages of the patients described by Bühler et al. 2 and Pfeiffer. 2

We re-examined one of these three patients when 5½ years old, but no exostoses were revealed on x-ray examination of the child. This finding apparently excludes the presence of LG syndrome, although the deleted region in our case overlaps the one described by Bühler et al. 2 (figure). This does not disprove the association hypothesis, since other factors may explain why subjects with the same chromosomal deletion show different phenotypes (for example, the presence of specific allele(s) in the monosomic region). It must be considered, however, that the absence of overlap of the 8q deleted segment in the subjects with LG syndrome can hardly be reconciled with the idea that a specific cytogenetic imbalance is causally related to the syndrome itself. Although the association hypothesis does not imply that all subjects with 8q deletions show LG syndrome (or a phenocopy), it remains to be explained how a specific phenotype can be determined by two quite distinct 8q deletions.

At present 'microcytogenetics' does not appear to clarify the genetics of LG syndrome. This field of research has shown a very promising beginning, but care must be taken in considering new correlations between cytogenetic and Mendelian anomalies.

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References


Genes for super-intelligence?

SIR,

Sofaer and Emery 1 find that the proportion of spectacular users is higher among Mensa members than among their same-sexed sibs. The authors note

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**Figure** Available observations of 8q deletions. Each line represents the monosomic region in individual patients. Numbers beside lines refer to the references.