both mothers were measured in duplicate on three occasions. Both showed a duplication of *PLP* (Fig. 1). No sequence changes were found when PCR products from each exon were screened using single strand conformation polymorphism analysis.

We also found that the PLP genes were intact after duplication. A restriction map produced using *Pst*I, *Eco*RI and *Xba*I (ref. 3) covering the entire coding region revealed no altered fragments in either individual or their mothers. Thus, the breakpoints fall outside the gene which must, therefore, be totally duplicated. One boy (JH) was more severely affected than the other. This may be due to the differing extent of the duplicated region which we have not yet been able to define.

A suggestion that increased dosage of *PLP* may cause PMD came from a patient with a large, cytogenetically visible, *de novo* duplication of Xq21–22 (ref. 8). The boy showed multiple abnormalities: muscular hypotonia, growth retardation, cryptoorchidism and a severe generalized disorder of myelination suggestive of PMD at autopsy. Dosage studies showed *PLP* to be within this large duplicated region[9].

These cases form a strong parallel with CMT1A, which generally involves a 1.5 Mb duplication of DNA including *PMP-22*. Point mutations of *PMP-22* have also been found in patients with CMT1A (refs 10,11) and decreased nerve conduction velocity, characteristic of CMT1 has been observed in three individuals with larger, cytogenetically visible duplications[12–14]. One of these patients[13], who had a complete trisomy for chromosome 17p resulting from an unbalanced translocation t(14;17)(p11;p11), had clinical symptoms of a peripheral neuropathy as well as the reduced nerve conduction velocities. There are parallels, therefore, between CMT1A and PMD in all three respects: point mutations, duplications and large cytogenetically visible duplications.

Why do point mutations and increased dosage produce such similar phenotypes? Neither mother of the two boys with PMD has any symptoms despite an increased dosage themselves. This may be due to selective survival of cells in which the normal chromosome is active. A possible explanation for the similar phenotypes is that both proteins act as part of a multi-component unit within myelin and the stoichiometry between the components is critical. However, no interacting molecules have yet been identified. It would be most interesting to establish whether other similar neurological disorders arise from mutations of the other components.

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Chromosome 4p16 and osteochondroplasias

Sir—We read with interest the recent articles in *Nature Genetics* by Velinov *et al.*[1] and Le Merrer *et al.*[2] establishing linkage of achondroplasia (ACH)[1,2] and hypochondroplasia (HCH)[2] near the telomere of chromosome 4p. We proposed recently a tentative location in 4p16 or 4q13 of the gene(s) responsible for osteochondrodysplasias[3]. This was based on our observation of a pericentric inversion in chromosome 4, with breakpoints at p16 and q13.2, in a patient with characteristic skeletal and extraskeletal manifestations of a lethal short rib-polydactyly syndrome (SRPS), one form of autosomal recessive osteochondrodysplasia. Rivas *et al.*[4] noted a similar chromosome 4 inversion (breakpoint at 4p16) in a family with thanatophoric dysplasia, an autosomal dominant osteochondrodysplasia. Thus, chromosome 4p16 appears to be related to other osteochondrodysplasias in addition to ACH and HCH.

These data raise important clinical and aetiologic questions about osteochondrodysplasias. The association of chromosomal rearrangements involving 4p16 with both SRPS[3] and thanatophoric dysplasia[4] raises the possibility of a close genetic basis for these two clinically distinct forms of osteochondrodysplasia. Evidence that ACH and HCH, also well distinguishable clinically, are due to defects in 4p16 strongly supports this possibility. We suggest that the distal short arm of chromosome 4 may contain several genes for osteochondrodysplasia, or (less likely) that these conditions result from different mutations of the same gene.

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