UNIPARENTAL DISOMY: A NOVEL MECHANISM FOR THALASSEMIA MAJOR

To the Editor:

We present here a remarkable case of simultaneous expression of two genetic diseases resulting in a rare genetic event. The 11p15.5 region contains several loci involved in genetic diseases including the β hemoglobinopathies as well as malignant processes, like the Wiedemann-Beckwith syndrome (WBS). The β globin locus has been extensively studied in recent years because it
The recent study of a large series of WBS patients has also shown that the WBS is a disorder of abnormal growth, characterized by macroglossia, abdominal wall defects, hypoglycemia, and abnormal craniofacial features. Most cases are sporadic, but in a few familial ones the disease segregates as a dominant trait; the carriers are then mainly female, suggesting that the WBS locus may be an imprinted gene, in which the paternal allele is more active than the maternal one. The disease would then result from an overriding of the normal imprinting.

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The propositus presented at birth with a typical WBS. During the first year of life, simultaneously with the apparition of tumors, he developed the classical symptoms of thalassemia major. The features of a thalassemic trait were found in the father's blood: microcytic polychromatia, hemoglobin (Hb) A2 5.2%, Hb F 2.1%. The hematologic parameters found in the mother were normal: mean cell volume (MCV) 98 fl, Hb A2 2.3%, Hb F < 1%. The mutation was identified by dot-blot hybridization, after polymerase chain reaction (PCR) amplification (Table 1). It was found in the homozygote state in the propositus and heterozygous in the father, whereas the mother was normal. The classical haplotypes were explored and demonstrated the same kind of discrepancy: propositus II/II, father 1/II, mother III/V1 (special emphasis should be given to the HincII sites within the β globin gene: propositus − +/− +, father − −/− +, mother −−/++). The parental relationships were confirmed by studying three markers of HLA (DQA1, DQB1, and DPBI) on chromosome 6 and the hypervariable region 3′ to the α globin gene on chromosome 16. All these markers disclosed both paternal and maternal contributions, as expected. Different alleles located on the short arm of chromosome 11 were explored: CAT, LDHA, PTH, CALCA, HBBC, INS/IGF2/TH, Hras1 (Fig 1A). The pattern obtained at three informative loci, namely CALCA, HBBC, INS, and INS, is given in Fig 1B. It shows clearly that the propositus failed to inherit maternal alleles. On the long arm only the CA repeat in 11qS35 was informative, displaying the contribution of both parents. A gene dosage was performed using a collagen type 1α1 probe (chromosome 17). The signal ratio confirmed the existence of two copies of the β globin locus.

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phenotypic as well as genotypic data. Therefore, uniparental isodisomy represents the most likely explanation as defined by Engel,7 in this case involving only part of the short arm of chromosome 11, where both globin and WBS loci are located. The loss of heterozygosity is usual in various tumoral tissues and was described in 11p in Wilms tumors.6 To our knowledge, its extension to the β globin locus, presence in peripheral blood cells, and expression as a thalassemia major have never been observed. Nevertheless, it is quite possible that such a process has existed without clinical expression because a double dose of a normal β globin gene of uniparental origin would probably be unapparent. Uniparental isodisomy as an explanation for the expression of recessive disorders is a rare event. Up to now, it has been proposed for chromosome 7 twice4,5 and chromosome 6.6 In all these cases, as in ours, some conditions are fulfilled. The involved chromosome carries a recessive pathologic trait with easily recognizable phenotype, linked to informative polymorphisms. Given the relative frequency of isodisomy for an autosome, and the frequency of normal segregation of a thalassemic defect, a case similar to the one described here must be extremely rare. In contrast to the somatic homozygosity regularly found in tumors, it raises the question of a germline event. Consistent with previous observations, the retention of paternal alleles3 argues for a genome imprinting process to give rise to WBS and associated pathologies. Favoring this hypothesis is the fact that the 11p loci found homozygotes in this case of WBS are actually superimposable or very close to imprintable segments of the mouse chromosome 7.9

REFERENCES


ACKNOWLEDGMENT

We thank Prof Jean-Claude Dreyfus for fruitful discussion of the manuscript. We also thank Dr M. Bonnet for patient referral, and the family for their cooperation. Supported by INSERM grants to the different Research Units, and by an EEC grant (TS2-0065-F[SP]).

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Uniparental disomy: a novel mechanism for thalassemia major [letter]

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