alleles (D2) carry two "intronic mutations", 1105G→C and 1391G→A. They suggested that these intron alterations might be "regulatory mutations" involved in regulation of GALT gene expression.

In the present work, we have described a new DNA alteration on Duarte alleles, the deletion of four nucleotides (GTCA) in the 5' promoter region of the GALT gene (−119del4). There is a high probability that this deletion is located in the transcription factor binding region. For this reason a computer search for potential regulatory DNA elements in the area of the deletion was performed.[10] Two *Homo sapiens* binding factors (activator proteins AP1 Q2 and AP1 Q4), which lose their binding motifs in Duarte (D2) alleles, were found. We conclude that the –119del4 promoter mutation is perhaps the main factor in Duarte allele enzyme activity reduction caused by a decrease in the synthesis of mRNA. This hypothesis will be tested further; however, Shin *et al*[6] reported that in competitive RT-PCR, the RNA level from homozygous Duarte (D2) cultured human lymphocytes was lower than that obtained from control cultured human lymphocytes.

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Familial congenital diaphragmatic hernia: is an imprinting mechanism involved?

EDITOR—Isolated congenital diaphragmatic hernia (ICDH) may be sporadic or familial. The mode of inheritance in familial cases (IFCDH) is a matter for debate and different patterns have been proposed. For example, multifactorial inheritance was suggested by Wolff[1] and by Norio *et al*.[2] However, autosomal recessive inheritance has been suggested in clinical studies[3–6] and also in animal studies.[7 8] Also, there have been various families reported to date in which other patterns of inheritance are possible (table 1).

If all the published pedigrees with familial CDH are analysed, autosomal dominant, autosomal recessive, and X linked inheritance patterns can be seen. We propose a hypothesis which unifies these various mechanisms, which is to consider imprinting as involved in the inheritance pattern of this condition.

In 1994, two non-consanguineous girls with isolated CDH and balanced translocations involving 8q22.3 were reported by Temple *et al*.[14] More recently, Tokuhara *et al*[15] have cloned the gene HFZ6 and localised it to 8q22.3-q23.1. HFZ6 corresponds to the human frizzled-6 gene and is a member of the family of frizzled genes that encode receptors for Wnt proteins, which are secreted proteins involved in cell-cell interaction during embryonic development and tumorigenesis.[16] Moreover, these frizzled genes are homologous to the *Drosophila frizzled* gene family, a group of homeobox genes determining morphogenesis and planar polarity phenotypes both in *Drosophila* and vertebrates.[17–19]

Frizzled genes have been thought to be related to spatial control during the embryological development of various structures, in particular the heart.[20] Other authors[21–24] and ourselves[25] have found that when CDH is accompanied by other anomalies, these usually involve the heart and CNS, suggesting a developmental association. Frizzled gene deletions have already been associated with other genetic disorders, such as Williams syndrome,[26] in which they could have a role in early brain developmental anomalies.

Table 1 Published isolated familial congenital diaphragmatic hernia (IFCDH) cases

Affected family members	*Possible mendelian inheritance mechanism involved*	*No assigned to the family in our study*	*No in prototype pedigree figures*	*References*
Two brothers and a maternal uncle	Sex linked recessive, autosomal dominant with incomplete penetrance	1,2	1a	9, 10
Two half brothers from the same mother	Sex linked recessive or dominant, autosomal dominant	3	1b	11
Father and daughter	Sex linked dominant, autosomal dominant	4	1c	12
Mother and son	Sex linked dominant or recessive, autosomal dominant	5	1d	13
Various affected family members in only one generation of a consanguineous kindred	Autosomal recessive	6	1e	5

As can be seen in the cases reported by Temple *et al*,[14] one girl inherited the cytogenetic defect from her mother, the translocation in the other girl was de novo, and uniparental disomy was excluded in both. This suggests the presence of a major gene involved in normal diaphragmatic development at this locus. Major genes are invoked when the development of complex structures is thought to be controlled by various genes, with one of them having a more important role in phenotype determination. In this case, if such a gene (for example, Hfz6) is involved, as suggested by the patients with balanced translocations, genomic imprinting could be involved in its regulation, with the maternal gene being normally expressed and the paternal gene being normally silenced, producing the disease phenotype when an abnormal gene is inherited from the mother. This could have happened in families 1, 2, 3, and 5 in table 1, as well as in the numerous cases reported by other authors[3 27–30] and ourselves[25] with two or more sibs affected. Although there are not many examples of these genes, the theoretical presence of a major gene regulated by imprinting is possible. Various genes, now clearly recognised as being regulated by the imprinting mechanism, initially had a poorly understood pattern of inheritance because of the apparently contradictory data. It is also known that many imprinted genes are involved in development,[31] such as the one we have mentioned here. There is evidence of imprinting of at least one of the frizzled gene family members, *Xfz3*, which is maternally expressed in *Xenopus.*[32] In humans, there is no clear evidence of imprinting on chromosome 8, but some authors have found different parental origin of a deletion in chromosomal region 8q24 in Langer-Giedion syndrome,[33 34] which is located contiguously to the chromosome band containing HZF6.

The case of Frey *et al*[12] (father to daughter transmission, family 4, table 1) could be explained if paternal uniparental disomy had occurred. This was not ruled out, unlike in the study of Temple *et al*,[14] where uniparental disomy of chromosome 8 was studied and excluded.

In spite of this evidence, we could not exclude the possibility that different patterns of inheritance could be occurring in different familial cases, as happens in other diseases. Consanguineous kindreds, such as those reported by Farag *et al*[4] and Mitchell *et al*[5] (table 1, fig 1E), could support our hypothesis but are more likely to represent other mechanisms of inheritance.

However, molecular and segregational analyses of more families are needed to verify this hypothesis.

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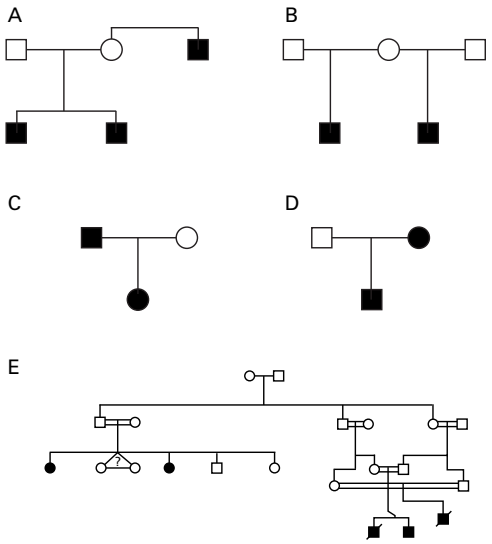

Figure 1 Family pedigrees. (A) IFCDH: two affected brothers and maternal uncle. (B) IFCDH: two affected half brothers of the same mother. (C) IFCDH: affected father and daughter. (D) IFCDH: affected mother and son. (E) Consanguineous kindred with IFCDH.

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