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REVIEW ARTICLE

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Parents of children with autosomal recessive diseases are not always carriers of the respective mutant alleles

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Abstract Classically, each parent of a child with an autosomal recessive disease has been considered to carry at least one copy of the abnormal allele. However, with the increasing ability to characterise the molecular basis of genetic diseases, several exceptions have been reported. The most frequent situation is that only one parent is a carrier of the mutation that is present in the patient in two copies either because of uniparental disomy or because of a de-novo mutation on the gene transmitted by the non-carrier parent. In order to give accurate genetic counselling, in particular when prenatal diagnosis is envisaged, molecular analysis of each of the parents of a child affected with an autosomal recessive disease must be routinely performed.

Introduction

As pointed out by Stern (1973), "By definition, a single recessive allele will not affect the phenotype of a person and only when both of the alleles at a locus are recessive is there any effect. Therefore, each parent of a child with a recessive trait must carry at least one copy of the recessive allele". This classical definition is the basis for genetic counselling of couples who have children affected by an autosomal recessive disease and who, if they are healthy, are given a 25% risk for each future pregnancy. However, with the possibility of verifying the carrier state of the parents of affected children in an increasing number of cases, it appears that, after ruling out non-paternity, there are rare but important exceptions to this rule.

New mutations

The mutation rate in humans is estimated to be on average $1–2\times10^{-8}$ per nucleotide per generation and is probably in an order of magnitude higher in males than in females (Crow 1995). A higher mutation rate among males has been implied to explain the paternal age effect (Crow 1995). However, recent studies of FGR3 and FGR2 mutations in the sperm cells from men of different ages have not found an increase in mutation that may explain the higher frequency of affected progeny (Crow 2003). The possibility of selection of mutant spermatogonia has been suggested for the FGR2 gene.

Mutations in the germ line

De novo mutations are easily detected in dominant disorders and in X-linked recessive diseases, since only one abnormal allele is necessary for clinical expression. For de novo autosomal recessive mutations to be detected, a patient must have inherited a mutant allele carried by one parent and a de novo germ cell mutation from the other. Therefore, statistically, it could be expected that de novo recessive mutations will be detected very rarely in the clinic. The probability for the simultaneous occurrence of the two events will be higher when the carrier frequency of the diseases is relatively high and/or if new mutations are frequent. Examples of such diseases are cystic fibrosis (a disease that is relatively frequent among Caucasians), spinal muscular atrophy and steroid 21-hydroxylase deficiency, disorders in which new mutations are frequent.

Cystic fibrosis

Even though the molecular diagnosis of cystic fibrosis has been available for many years and a large number of patients' families have been tested, there are few reports of cases of de novo mutations. However, whereas de novo mutations either have never been found or have been reported as a single case for other genes with mutation rates similar to that of the cystic fibrosis transmembrane conductance regulator (CFTR) gene, de novo mutations in the CFTR gene itself have been demonstrated in four instances

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among patients affected with cystic fibrosis (Casals et al. 1998; Cremonesi et al. 1996; White et al. 1991).

Adrenal hyperplasia attributable to steroid 21-hydroxylase deficiency

Congenital adrenal hyperplasia, caused by the deficiency of the enzyme steroid 21-hydroxylase is an inborn error of steroidogenesis in which cortisol is not sufficiently produced by the adrenal cortex (White and Speiser 2000). Classic 21-hydroxylase deficiency occurs in about 1 in 14,000 live births and is the most common cause of genital ambiguity in females. Prenatal exposure to excess androgens results in virilization of the female fetus, whereas newborn males have normal genitalia. Postnatally, untreated females and males present with signs of androgen excess. Three-quarters of classic 21-hydroxylase deficiency cases do not effectively synthesize aldosterone and are salt-wasting, a condition that is potentially fatal. An allelic variant of classic 21-hydroxylase deficiency, viz. non-classic 21-hydroxylase deficiency, is associated with a milder enzymatic defect. The 21-hydroxylase enzyme is encoded by the gene CYP21, which has a closely neighbouring homologous pseudogene, CYP21P. Mutations in the CYP21 gene, causing 21-hydroxylase deficiency, are common and occur mainly because of two mechanisms: gene deletion and gene conversion. It has been estimated that approximately 95% of the mutant alleles have been generated through intergenic recombination: 20% of the alleles have a 30-kb deletion secondary to an unequal crossing-over, whereas the other 75% of the alleles are generated by gene conversions (White and Speiser 2000).

Table 1 De novo mutations among patients with steroid 21-hydroxylase deficiency. The estimates are minimal since, in most cases, the family data were not available for all alleles

Country	No. patients	No. mutations de novo (%)	References
Spain	101	0	Lobato et al. 1999
France	65	0	Barabat et al. 1995
Lebanon	48	0	Delague et al. 2000
Austria	67	0	Baumgartner-Parzer et al. 2001
Netherlands	370	1	Stikkelbroek et al. 2003
Sweden	<186	1	Wedell et al. 1994
Germany	<306	2	Krone et al. 2000
Brazil	228	2	Bachega et al. 1998
USA	<176	2 (1.1)	Speiser et al. 1992
Denmark	136	2 (1.5)	Ohlsson et al. 1999
Slovenia[a]	63	1 (1.6)	Dolzan et al. 2003
Argentine	57	1 (1.8)	Dain et al. 2002
Finland[a]	86	2 (2.3)	Levo et al. 2001
Mexico	74	8 (10.8)	Ordonez-Sanchez et al. 1998
Japan	46	4 (8.7)	Tajima et al. 1998
Japan	36	3 (8.3)	Asanuma et al. 1999
Total	2715	29 (1.1)	–

[a]Family data were available for all the alleles

In a summary of several population surveys of patients with steroid 21-hydroxylase deficiency originating from various part of the world (Table 1), de novo mutations were found in 1.1% of the alleles (29/2715). This represents a minimal estimate, since DNA from the parents of the affected patients was not always available for examination. According to the mean allele frequency in those populations, the mutation rate was estimated to be 2×10^{-4} (Tusie-Luna and White 1995). The high frequency of de novo mutations was confirmed by direct analysis of sperm and leukocytes of normal males (Tusie-Luna and White 1995). Deletions were detected in sperm DNA samples with a frequency of 1×10^{-5} to 1×10^{-6} and gene conversions in leukocytes and sperm DNA with a frequency of 1×10^{-3} to 1×10^{-4}. Whereas the percentages of de novo mutations were in a similar range in most populations studied, there were two striking exceptions: Japan (8.5%) and Mexico (10.8%; Asanuma et al. 1999; Ordonez-Sanchez et al. 1998). In Japan, the prevalence of steroid 21-hydroxylase deficiency is known (1:18,000 live births), being in the same range as in other populations (White and Speiser 2000). Therefore, the rate of de novo mutations among Japanese patients suggests a high mutation rate for CYP21 in this population.

Spinal muscular atrophy. Spinal muscular atrophy (SMA) is an autosomal recessive disorder characterized by symmetric proximal weakness and caused by the degeneration of the anterior horn cells of the spinal cord (Ogino et al. 2002). SMA has an estimated incidence of 1/10,000 live births with a carrier frequency of 1/40. The most frequent form of the disease (type I, Werdnig-Hoffmann) is characterized by early onset in infancy with weakness and hypotonia and death because of respiratory failure around the age of 2. In the SMA critical region, a large inverted repeat segment includes two almost identical forms of the survival motor neurone (SMN) gene SMN1 and SMN2. Most of the typical cases of SMA cases lack both copies of SMN1 as the result either of a deletion secondary to an unequal crossing over or of a gene conversion to SMN2. These events are relatively frequent and, in a summary of several studies, de novo mutations were observed in 1.5% of the patients affected with SMA (10 out of 1184 alleles; Lefebvre et al. 1998; Wirth et al. 1997). From those data, the overall mutation rate in the SMN gene was calculated to be $\mu=8.6\times10^{-5}$.

Somatic new mutations

Loss of heterozygosity has been described as a frequent mechanism in the context of cancer; however, it seems to be an uncommon cause of recessive diseases. One example is a patient who was affected with thalassemia intermedia and who was heterozygous for a mutation inherited from his father, while his mother was not a carrier. Molecular studies of the patient revealed that he also had a somatic mosaicism for a deletion on the maternal allele (Badens et al. 2002). This finding explained both the un-

usual inheritance of the disease and its relatively mild clinical presentation.

Uniparental disomy

Inheritance of both parental genomes is essential for normal growth and development. In mice and, later, in men, genes were demonstrated that were imprinted and expressed only from either the maternal or the paternal chromosome. Engel (1980) was the first to suggest the possibility that some of human pathology (in particular, growth retardation) may be associated with uniparental disomy (UPD). Molecular studies have demonstrated that UPD exists and is responsible for some pathology and has also been observed as an incidental finding in normal individuals (Englel 1998). The prevalence of UPD has been estimated according to the frequency of the syndromes caused by imprinting defects. The population frequency has been estimated at 1/80,000 for chromosome 15, at 1/75,000 for

Table 2 Examples in which uniparental disomy as the cause of an autosomal recessive diseases has been established (*M* maternal, *P* paternal)

Chromosome number	Disease	Type of disomy	References
Chromosome 1			
	Epidermolysis bullosa	P, M	Pulkkinen et al. 1997; Takizawa et al. 1997
	Pycnodysostosis	P	Gelb et al. 1998
	Congenital insensitivity to pain	P	Miura et al. 2000; Indo et al. 2001
	Chediak-Higashi	M	Dufourcq-Lagelouse et al. 1999
	Retinal dystrophy	P	Thompson et al. 2002
	Retinitis pigmentosa	P	Rivolta et al. 2002
Chromosome 2			
	Retinal dystrophy	P	Thompson et al. 2002
	Steroid 5-alpha-reductase 2 deficiency	P	Chavez et al. 2000
	Severe congenital hypothyroidism	M	Bakker et al. 2001
	Trifunctional protein deficiency	M	Spiekerkoetter et al. 2002
	Congenital hypothyroidism	M	Bakker et al. 2001
Chromosome 4			
	Abetalipoproteinemia	M	Yang et al. 1999
	Ellis-van Creveld	M	Thompson et al. 2002
Chromosome 5			
	Spinal muscular atrophy	P	Brzustowicz et al. 1994
Chromosome 6			
	Steroid 21-OH deficiency	P, P	Lopez-Gutierrez et al. 1998; Spiro et al.1999
	C4 deficiency	P	Welch et al. 1990
	Methylmalonic acidemia	P	Abramowicz et al. 1994
Chromosome 7			
	Cystic fibrosis	M, M	Beaudet et al. 1991; Hehr et al. 2000
		M, P	Spence et al. 1988; Voss et al. 1989
	Congenital chloride diarrhea	P	Hoglund et al. 1994
	Primary ciliary dyskinesia	P	Bartoloni et al. 2001
	Osteogenesis imperfecta II	M	Spotila et al. 1992
Chromosome 8			
	Lipoprotein lipase deficiency	P	Benlian et al. 1996
Chromosome 9			
	Cartilage hair hypoplasia	M, M	Sulisalo et al. 1997
	Leigh syndrome	M	Tiranti et al. 1999
Chromosome 11			
	Thalassemia	P	Beldjord et al. 1992
Chromosome 13			
	Deafness, Connexin 26	M, M	Álvarez et al. 2003
Chromosome 15			
	Bloom syndrome	M	Woodage et al. 1994
Chromosome 17			
	Thrombasthenia	M	Jin et al. 1996

chromosome 11 and at 1/1,250,000 for chromosome 6 (Kotzot 1999). UPD may reveal an autosomal recessive mutation present on the chromosome involved. The probability of such an event should be the product of the carrier frequency and the occurrence rate of UPD of the chromosome on which the gene is located. However, in the case of rare mutations, the proportion of cases attributable to UPD should be higher than that for relatively frequent disorders. The first report of UPD as a cause of a recessive disease was in cystic fibrosis. A patient homozygous for the mutation delta F508 was born to a father who was not a carrier of the mutation (Spence et al.1988). Molecular studies revealed that the child had inherited two copies of the same chromosome 7 that carried the CFTR mutation from his mother and no copy of the paternal chromosome 7. Meanwhile, other patients affected with cystic fibrosis were reported with the same type of inheritance, the isodisomy being either maternal or paternal. In the last few years, UPD has been diagnosed in more than 25 other diseases, mostly in single cases (Pulkkinen et al. 1997; Takizawa et al. 2000; Gelb et al. 1998; Miura et al. 2000; Indo et al. 2001; Dufourcq-Lagelouse et al. 1999; Thompson et al. 2002; Rivolta et al. 2002; Chavez et al. 2000; Bakker et al. 2001; Spiekerkoeter et al. 2002; Yang et al. 1999; Brzustowicz et al. 1994; Lopez-Gutierrez et al. 1998; Spiro et al. 1999; Welch et al. 1990; Abramowicz et al. 1994; Beaudet et al. 1991; Hehr et al. 2000; Voss et al. 1989; Hoglund et al. 1994; Bartoloni et al. 2002; Spotila et al. 1992; Benlian et al. 1996; Sulisalo et al. 1997; Tiranti et al. 1999; Beldjord et al. 1992; Álvarez et al. 2003; Woodage et al. 1994; Jin et al. 1996; Table 2).

The distribution of the chromosomes on which mutations have been revealed by UPD does not appear to be at random. Whereas four and more different diseases were reported in which children were born because of UPD of chromosomes 1, 2 and 7, there have been no reports of such situations for several other chromosomes. Comparing this list with the cases of UPD reported in the literature, several differences are striking. Many cases of UPD have been reported in acrocentrics, whereas there are few cases of autosomal recessive disorders revealed by UPD on those chromosomes. Chromosome 15 UPD was described in several hundred cases with Prader Willi syndrome or Angelman syndrome but only in a single case of autosomal recessive disease, Bloom syndrome (Woodage et al. 1994). For the other acrocentrics, two cases of deafness attributable to maternal UPD of chromosome 13 leading to homozygozity of the 35delG mutation in connexin 26 have been reported (Álvarez et al. 2003) and there is only one case of chromosome 14 UPD in which an autosomal recessive disease was reported (Pentao et al. 1992). In the report of Pentao et al. (1992), the child presented with achromatopsia suggesting homozygosity of a recessive gene but, up to now, whereas two other loci for the disease have been delineated, the presence of a locus on chromosome 14 has not yet been established. This relatively small number of autosomal recessive diseases revealed by UPD of the acrocentric chromosomes is surprising, since many genes responsible for autosomal recessive diseases have previously been characterised.

Another difference between the present list and the cases of UPD reported in the literature is the distribution of parental origins. In a survey of all reported cases, a significant preponderance of maternal versus paternal UPD has been noted with an approximate ratio of 3:1. Among the cases in which an autosomal recessive diseases has been revealed by a UPD, the ratio between maternal and paternal origin is close to one.

De novo mutation and uniparental disomy

The simultaneous occurrence of a new mutation in one of the gametes and then a UPD for the chromosome is expected to be extremely rare but has been described in one instance. A child affected with maple syrup urine disease (MSUD) was found to be homozygous for a 10-bp deletion in the MSUD2 gene, although neither parent carried the deletion (Lebo et al. 2000). The deletion was the result of a de novo event prior to maternal meiosis I followed by non-disjunction in maternal meiosis II resulting in UPD and two copies of the mutant allele.

Conclusion

In recent years, with the increasing ability of the performance of molecular analysis in families of affected children, it has become apparent that autosomal recessive diseases may sometimes occur even though only one parent is a carrier of a recessive mutation or when neither parent is a carrier. Some situations appear to be extremely rare but some are more common, such as de novo mutations or uniparental disomy. For some of the diseases, the rate of de novo mutations is clinically significant because of the mechanism of the mutations. For SMA and steroid 21-hydroxylase deficiency, one of the parents is not a carrier in more than 1% of the patients. The mutation rate seems to be higher for CYP21 than for SMN 1; however, since the test for SMN carrier detection is still difficult to perform and is carried out only in few laboratories, the number of families examined is still small and only larger numbers will allow conclusions to be made. For CYP21, differences in mutation rates appear to exist between population; this should be studied further.

The situations described in this review demonstrate that, in disorders in which the molecular basis is known, a molecular analysis of each of the parents must be the rule in order to give accurate genetic counselling. This is particularly relevant when prenatal diagnosis by using linkage is envisaged, since such studies rely on the assumption that both parents are carriers. Another important situation is when the affected individual is homozygous for a mutation and presents with clinical symptoms that are not usually part of the classical disease, since the additional symptoms may be related to UPD.

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