Genetic factors in lissencephaly syndromes: a review

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Abstract. Lissencephaly is a sign of various genetic and non-genetic conditions and a constant feature in the so-called lissencephaly syndromes. Type I lissencephaly in the Miller-Dieker syndrome (MDS) and the isolated lissencephaly sequence (ILS) is differentiated from type II lissencephaly in the Walker-Warburg (hydrocephalus, agryria, retinal dysplasia with or without encephalocele, HARD + E) syndrome and related conditions (e.g. muscle-eye-brain syndrome). In about 90% of patients with MDS structural defects have been confirmed in the short arm of chromosome 17 (p13.3), detectable by classical cytogenetic methods, fluorescence in situ hybridisation (FISH), or molecular genetic techniques. The identification of unbalanced inversions and translocations is of particular importance because of the risk of their recurrence, while deletions and ring chromosomes are mainly sporadic. Recently, submicroscopic deletions have also been reported in ILS, providing evidence that lissencephaly in MDS and ILS is caused by deletions of the same gene(s) in 17p13.3 and that MDS may be considered to be a “contiguous gene syndrome.” Syndromes featuring lissencephaly type II (HARD + E and related conditions) are most probably autosomal-recessively inherited. Neither the location of the genes involved nor the nature of the mutations are known at present. It is also unknown whether HARD + E and muscle-eye-brain syndrome are allelic.

Key words: Lissencephaly – Miller-Dieker syndrome – Isolated lissencephaly sequence – Walker-Warburg syndrome – HARD + E syndrome – Muscle-eye-brain syndrome

Introduction

Lissencephaly is a rare defect of early brain development. The pathological and clinical characteristics are reviewed elsewhere in this issue. Lissencephaly has been reported in a number of genetic and non-genetic conditions and is a constant feature of the so-called lissencephaly syndromes. Mainly on the basis of morphological criteria, several types of lissencephaly have been differentiated [4, 9] (Table 1), types I and II being well established and generally agreed upon. In this paper, some genetic aspects of the clinically most important lissencephaly syndromes will be reviewed with special reference to diagnosis and genetic counselling.

During the last decade our understanding of the causes of some lissencephaly syndromes, namely Miller-Dieker syndrome (MDS) and isolated lissencephaly sequence (ILS), have improved considerably, mainly due to the outstanding contributions of the two collaborating groups of Dobyns and coworkers, Indianapolis, and Ledbetter and coworkers, Houston (see references).

Type I lissencephaly
Miller-Dieker syndrome

First described by Miller in 1963 [23] and Dieker et al. in 1969 [7] in two families, MDS was originally believed to be an autosomal recessive condition following the observation of additional familial cases and parental consanguinity [25]. Dobyns et al. [8, 9] were the first to identify cytogenetic abnormalities involving 17p13 in several MDS families including the ones reported by Miller and Dieker.

Recently, Dobyns et al. [12] reported cytogenetic and molecular genetic findings in a series of 27 patients from 25 families. Conventional chromosome analyses using high-resolution banding revealed deletions of band 17p13 in 14 out of 25 probands. Three of these deletions resulted from familial rearrangements (reciprocal translocations and pericentric inversions); the remaining were obviously de novo events including a ring chromosome and a dicentric translocation. A number of patients reported earlier were included in this series [15, 29, 30]. There are at least
two additional published patients with ring chromosomes 17 leading to the MDS phenotype [2, 28].

In a series of papers, Ledbetter and coworkers [1, 18–20] reported the development of molecular genetic approaches to identify submicroscopic deletions in MDS and later ILS [21]. Using a panel of 12 anonymous DNA-markers mapped to 17p13 (10 at subband p13.3), deletions of variable sizes, most of them rather large, were demonstrated in cytogenetically normal patients by restriction fragment length polymorphisms (RFLP) or somatic cell hybrid analysis. Two highly polymorphic (14 alleles) VNTRs (variable number of tandem repeats) deleted in MDS proved particularly useful in clinical diagnosis. Using primers constructed according to unique sequences flanking the polymorphic repeat, polymerase chain reaction (PCR) produces variable-sized amplification products corresponding to the copy number of the repeat unit [24]. The alleles can be visualised directly on an ethidium-stained agarose gel. This technique allows simple and rapid confirmation of deletions, providing there is an informative constellation.

The molecular dissection of the MDS critical region facilitated another promising diagnostic approach: fluorescence in situ hybridisation (FISH). Kuwano et al. [18] used two biotinylated cosmid probes from 17p13.3 to demonstrate "half cryptic" as well as "cryptic" translocations (i.e. translocations not visible on high-resolution banding preparations) in MDS families. In the meantime, such probes are commercially available, e.g. by Oncor. At a time where FISH is becoming increasingly popular in many cytogenetic labs, it is probably the method of first choice in the diagnosis of MDS when conventional techniques have shown "normal" chromosomes. Furthermore, it is at present the only technique available to confirm or exclude "cryptic" balanced parental rearrangements when a molecular deletion was diagnosed in a patient with MDS.

With currently available techniques deletions of variable size of 17p13.3 have been confirmed in 22 out of 25 patients with MDS [12, 18]. In contrast to other microdeletion syndromes like Prader-Willi syndrome or Angelman syndrome, the parental origin of the deletion did not obviously influence the phenotype. Both maternally and paternally derived deletions were observed. The size of these structural defects suggests the conclusion that MDS is a so-called "contiguous gene syndrome", that means a condition resulting from deletion of several independent genes physically contiguous on 17p13.3. Ledbetter et al. [21] therefore expected to find patients with individual features of MDS, such as lissencephaly, due to smaller deletions or point mutations (see below).

Diagnosis. With the availability of computer tomography (CT) and magnetic resonance imaging (MRI), lissencephaly is today diagnosed more reliably and also more frequently than some years ago. Once lissencephaly has been confirmed, MDS can be suspected if characteristic craniofacial abnormalities are present, some of which (microcephaly, bitemporal hollowing, micrognathia) are considered to represent the lissencephaly sequence. Patients with MDS usually exhibit, in addition, midline calcifications, a high forehead, a short nose, upturned nares and other anomalies (Fig. 1). Detailed accounts are given in several papers by Dobyns et al. Additional malformations may be present in unbalanced translocations depending on the chromosomes involved and in unbalanced inversions depending on the breakpoints and position of crossover. A conventional chromosome analysis including high-resolution banding is mandatory whenever MDS is suspected. For this type of chromosome study it is very important to indicate the diagnosis specifically, since structural defects in MDS as in other microdeletion syndromes will probably remain undiagnosed in a routine cytogenetic workup. "Normal" chromosomes do not exclude MDS. The next diagnostic steps are FISH with the appropriate probes and/or PCR-based analysis of the VNTRs as mentioned above. Other molecular genetic techniques may be necessary in occasional cases. When deletions, especially those of large size, are identified, parental balanced structural rearrangements have to be considered and investigated because of their potentially high recurrence risk. FISH is particularly helpful in the detection of cryptic parental structural anomalies.

Genetic counselling. In the light of the recent advances in the diagnosis of MDS, no convincing evidence remains for autosomal recessive inheritance. The recurrence risk of MDS is probably high with parental balanced translocations and inversions. Prenatal diagnosis, preferably by chorionic villus sampling, is clearly indicated and allows a definite diagnosis. De novo deletions, either microscopically visible or submicroscopic, should have only a low recurrence risk. The possibility of germinal mosaicism, however, should be kept in mind. A given deletion present in the index case might even be excluded prenatally by appropriate techniques if so chosen by the parents. Reliance on ultrasonographic evaluations of prenatal fetal growth and movements as well as amount of amniotic fluid and brain development should be restricted to occasional cases. In conclusion, the new diagnostic tools have significantly improved our ability to support affected families.

Isolated lissencephaly sequence

As discussed recently in detail by Dobyns et al. [13], ILS is the diagnosis in patients with type I lissencephaly and

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<thead>
<tr>
<th>Syndrome</th>
<th>Type</th>
<th>Cause</th>
</tr>
</thead>
<tbody>
<tr>
<td>Miller-Dieker syndrome</td>
<td>I</td>
<td>Del 17p13.3 or unknown</td>
</tr>
<tr>
<td>Isolated lissencephaly sequence</td>
<td>I</td>
<td>Del 17p13.3, autosomal recessive, exogenous, unknown</td>
</tr>
<tr>
<td>Walker-Warburg and related syndromes (HARD + E)</td>
<td>II</td>
<td>Autosomal recessive</td>
</tr>
<tr>
<td>Cerebro-oculo-muscular syndrome</td>
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a Modified from [10]