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Molecular genetics in fetal neurology

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SUMMARY

Brain malformations, particularly related to early brain development, are a clinically and genetically heterogeneous group of fetal neurological disorders. Fetal cerebral malformation, predominantly of impaired prosencephalic development namely agenesis of the corpus callosum and septo-optic dysplasia, is the main pathological feature in fetus, and causes prominent neurodevelopmental retardation, and associated with congenital facial anomalies and visual disorders. Differential diagnosis of brain malformations can be extremely difficult even through magnetic resonance imaging. Advances in genomic and molecular genetics technologies have led to the identification of the sonic hedgehog pathways and genes critical to the normal brain development. Molecular cytogenetic and genetic studies have identified numeric and structural chromosomal abnormalities as well as mutations in genes important for the etiology of fetal neurological disorders. In this review, we update the molecular genetics findings of three common fetal neurological abnormalities, holoprosencephaly, lissencephaly and agenesis of the corpus callosum, in an attempt to assist in perinatal and prenatal diagnosis.

1. Introduction

Genomic and genetic technology has advanced rapidly in the last decade, resulting in better characterization and understanding of the genetics of neurological disorders, with potential for treatment, and ultimately prevention. The etiology of fetal brain malformation is very heterogeneous; besides environmental factors, the most common cause is attributed to genetic conditions. Clinical assessment of fetal neurological structural abnormalities is well facilitated by ultrasound and magnetic resonance imaging (MRI). It is hoped and predicted that advances in fetal brain imaging will provide intermediate phenotypes for genetic studies, but its relevance for prenatal diagnosis of fetal neurological disorders remains unclear. In this regard, the advancement in genomic medicine by microarray-based diagnosis is of particular interest for neurodevelopment disorders, because it allows better delineation of novel genome-wide submicroscopic chromosomal abnormalities in early human development. The recognition of the genetic origin of brain malformations is important not only for the management of the identified fetus, but also for the potential genetic implications for other family members and subsequent pregnancies.

Whereas the risk of any single fetal neurological disorder is low, large-scale population-based studies including subjects across a wide range of phenotypes provide better information about the prediction for developing any undesirable pathology from a given chromosomal or genetic anomaly. For example, the introduction of chromosomal microarray analysis allows a comprehensive genome-wide screening of patients with holoprosencephaly (HPE). Microarray analysis has identified pathogenic copy number variants (CNVs) in more than 10% of all individuals with HPE.[1,2] These CNVs include loci already known to be associated with HPE, as well other loci whose relationship to HPE is less well understood. Microarray-comparative genomic hybridization (aCGH) has largely replaced classical cytogenetic testing. In addition, phenotype–genotype data sharing exemplified by *GeneReviews*, OMIM and DECIPHER have shifted the current clinical practice to adopt both phenotype-first and genotype-first approaches for fetal neurology. This has major implications for both prenatal screening and diagnostic testing. In this review, we focus on the latest molecular genetics findings of three common fetal neurological abnormalities, namely holoprosencephaly, lissencephaly and agenesis of the corpus callosum (ACC).

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2. Holoprosencephaly

Holoprosencephaly is a severe fetal brain malformation caused by a failure of cleavage of the embryonic forebrain or prosencephalon.[3] It is the most common structural defect of the forebrain in humans, seen in about 1 in 250 conceptuses; the prevalence at birth varies from 0.48 to 1.2 per 10,000 live births.[4,5] There are three classical types of HPE with decreasing severity: the alobar, semilobar and lobar types, with the anterior portion of the brain being least well formed in the severe case. HPE is also associated with midline abnormalities including facial anomalies, ranging from anophthalmia, cyclopia, proboscis, midline/bilateral cleft lip/palate, absent septum pellucidum and corpus callosum. HPE is an etiologically heterogeneous disorder. Both genetic and environmental factors are known to cause HPE, and genetic causes are responsible for about 20% of live birth cases.[6] Children with HPE may be presented with developmental delay, neurological deficit, endocrine problem such as diabetes insipidus, adrenal hypoplasia, hypogonadism, thyroid hypoplasia and growth hormone deficiency. The genetic causes of HPE can generally classified under the categories of chromosomal, and monogenic (syndromal and isolated) abnormalities.

The overall genotype–phenotype correlation has been extensively reviewed by Solomon et al.[7] In general, patients with *ZIC2* mutations display a distinctive phenotype with bitemporal narrowing, upslanting palpebral fissures, a short nose with anteverted nares, a broad and well demarcated philtrum, and large ears. But microduplication of the *ZIC2* gene is not associated with holoprosencephaly.[8] Patients with *SIX3* mutations tend to have more severe HPE than other patients with non-syndromic, non-chromosomal HPE. Step-by-step recommendations for molecular genetics evaluation are reviewed by Pineda-Alvarez et al.[9]

2.1. Chromosomal

Abnormalities of chromosome number range from 32% to 41% of patients with HPE, in which trisomy 13 accounts for up to 75% of cases and triploidy for up to 20%, whereas trisomy 18 is much less commonly seen in conjunction with HPE and accounts for 1–2% of cases.[6] Rare chromosomal abnormalities are found recently related with HPE, such as partial trisomy 3p and partial monosomy 11q,[10] monosomy 1p36,[11] and balanced reciprocal translocation between chromosomes 7 and 8.[12] Thus chromosome analysis is strongly indicated in cases with HPE, either by conventional karyotyping or by multiplex ligation-dependent probe amplification. To allow a better delineation of novel chromosomal abnormalities with the aim of identifying new HPE genes, higher resolution techniques, such as aCGH, have become well adapted in the clinical setting. Currently, aCGH studies have adapted both a phenotype-first approach, examining patients with HPE for mutations in, or deletions of, known HPE genes, and also a genotype-first approach, studying individuals with deletions of known and candidate HPE loci followed by correlation with the presence or absence of HPE. A large cohort study by Rosenfeld et al.[13] of 136 individuals in whom aCGH identified a deletion of one of the 35 HPE loci supports the hypothesis that the interaction of multiple genetic and environmental factors is required to result in HPE.

2.2. Syndromal

HPE can be a component of multiple malformation syndromes. Approximately 18–25% of individuals with HPE have a mutation in a single gene causing syndromic HPE. Table 1 lists some of the more commonly documented syndromes with HPE. For details please refer to *GeneReviews* (http://www.ncbi.nlm.nih.gov/books/NBK1530/).

2.3. Isolated

This form of HPE can be inherited in a mendelian fashion, usually in an autosomal dominant (AD) manner, with penetrance of about 70%.[14] To date, more than 13 genes and loci have been associated with HPE, and eight identified genes are listed in Table 2 (modified from Roessler and Muenke[15]). These genes have already been applied in prenatal diagnosis, analyses by fluorescence in-situ hybridization (FISH), whole genome oligo-based aCGH, or coding region sequence analysis. Other loci serve as susceptibility factors, with unknown molecular function including candidate loci: *HPE1* at 21q22.3, *HPE6* at 2q37.1–q37.3, *HPE8* at 14q13, *HPE 10* at 1q41–q42; for *HPE8*, three genes, *SNX6*, *NPAS3* and *C14ORF11*, have been identified as potential candidates for HPE[16] and have been suggested to be the ultimate target of treatments.

3. Lissencephaly

Lissencephaly is a severe neurological malformation in which the surface of the brain is smooth with either complete absence of gyri (agyria) and sulci or only a few broad gyri (pachygyria) and a few shallow sulci. Lissencephaly, due to disorders of neuronal migration, can be undermigration, overmigration or ectopic migration of neurons between 12 and 20 weeks gestation, and is generally divided into two categories: classic lissencephaly (also known as type 1 lissencephaly), and cobblestone complex (also known as type 2 lissencephaly), with an estimated incidence of 1.2 in 100,000 births and 1 in 100,000 births respectively.[17] Additionally, there are three less common types, suggested to be variant lissencephaly: lissencephaly with agenesis of the corpus callosum (XLAG), lissencephaly with cerebellar hypoplasia (LCH), and microlissencephaly.[18]

3.1. Classic lissencephaly

Classic lissencephaly results from undermigration of neurons. It is characterized by agyria or pachygyria. There are three genes

Table 1
Malformation syndromes in which holoprosencephaly is a characteristic feature.

Syndrome	Phenotype OMIM number	Chromosome location	Gene	Gene OMIM number	Inheritance	Animal model	Associated features	Reference
Pseudotrisomy 13	264480	13q32, 5q35	*FBXW11*	605651	AR	None	Polydactyly, ventricular septal defect, microphthalmia	Koolen et al.[42]
Pallister–Hall	146510	7q14.1	*GLI3*	165240	AD	None	Hypothalamic hamartoma, hypopituitarism, polydactyly	Johnston et al.[43]
Smith–Lemli–Opitz	270400	11q13.4	*DHCR7*	602858	AR	Mouse, rat	Microcephaly, ptosis, syndactyly	Yu et al.[44]
Velocardiofacial	192430	22q11.21	*TBX1*	602054	AD	Mouse	Cleft palate, congenital heart disease, short stature	Paylor et al.[45]

AR, autosomal recessive; AD, autosomal dominant.