Brain Imaging and Genetic Risk in the Pediatric Population, Part 1

Inherited Metabolic Diseases

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KEYWORDS

• Brain imaging • MRI • Magnetic resonance • Inborn errors of metabolism • Genetics • Metabolic disorder

KEY POINTS

- Inherited metabolic diseases (IMD) form a group of disorders, mostly genetically inherited, caused by abnormal protein formations.
- One strategy to increase the accuracy of neuroimaging in IMD is to compare the genetic information (genotype) with the imaging phenotype detected by MRI (MR phenotype).
- Some MR phenotypes are related to specific gene mutations, such as bilateral hypertrophy of inferior olives in patients harboring POLG and SURF1 mutations, and central lesions in the cervical spinal cord in nonketotic hyperglycinemia patients harboring GLRX5 gene mutation.
- From a neuroimaging point of view, a desirable scenario of the future could be using brain imaging, such as advanced MRI, as a biomarker (MR phenotype) to predict the most probable genetic abnormality of a specific neurologic disease (genotype).

INTRODUCTION

Significant advances in imaging of the structure and function of the brain, brainstem, and cerebellum have been made in the last decades.[1–6] High-resolution MRI and diffusion tensor imaging have been extensively used in both clinical and neurosciences settings, expanding and redefining the applications of modern neuroimaging techniques. An example of this issue can be clearly found in the malformation of the cerebral cortex, in which development of MRI technology associated with a better understanding of embryology, neurodevelopment, and neurogenetics has dramatically changed the way researchers classified these diseases.[7–10]

Equal achievements occurred in our understanding of the human genome and its role in normal and abnormal development of the central nervous system (CNS).[11–15] From a biological perspective, the identification of a genetic abnormality can improve our understanding of the mechanism of specific diseases. From a clinical

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perspective, a genetic diagnosis could optimize diagnosis, prognosis, and treatment of neurologic disorders.

In this context, imaging and genetic studies have been predominant in the investigation of many pediatric neurologic disorders, particularly congenital malformations of the CNS (CMCNS) and inherited metabolic disorders (IMD).[6,16–21] Linking genetic data and neuroimaging phenotype is an emerging approach in neuroscience to better understand the complex imaging appearance of these disorders. From a neuroimaging point of view, a desirable scenario of the future could be using brain imaging, such as advanced MRI, as a biomarker (MR phenotype) to predict the most probable genetic abnormality of a specific neurologic disease (genotype). This approach could be useful to both neuroscientists (better genetic-neuroimaging integration) and clinical physicians (better approach to neurologic diseases), making imaging a better diagnostic tool for more effective treatment and prognosis definition.

In this article, the genotype-MR phenotype correlation of the most common or clinical relevant IMD and CMCNS in the pediatric population are reviewed. Although many disorders could be included in this review, the data focus on the most commonly diagnosed diseases and those in which the neuroimaging abnormalities are better defined. The PubMed/Medline database was searched with a combination of key words such as “genotype-phenotype correlation,” “genotype-imaging correlation”, and “neuroimaging-genetic correlation” in both IMD and CMCNS. The searches were limited to articles in English and those with abstracts. After the searches were conducted, the abstracts of the returned articles were examined, to determine their applicability for review. Relevant studies were defined liberally to be those that included any discussion about correlation of neuroimaging and a genetic abnormality in both IMD (part 1) and CMCNS (part 2 elsewhere in this issue). A review of the general rules of genotype-phenotype correlation is included in this review (part 1), because we believe that knowledge of the principles of medical genetics is essential for every neuroscientist (including radiologists).

GENOTYPE-PHENOTYPE CORRELATION

In neurosciences, few topics have advanced as fast as neurogenetics.[11–15] Data from the last 20 years in recombinant DNA technology and polymerase chain reaction (PCR) linkage studies significantly increase the number of neurologic disease genes identification, but identifying genes for both autosomal dominant and recessive diseases has been challenging. However, the advent of next-generation sequencing (NGS) with the whole genome sequencing (WGS), target sequencing, and whole exome sequencing (WES) has dramatically changed this scenario. These new techniques are emerging as a tool to facilitate cost-effective molecular diagnoses in routine clinical care of these disorders.

As a rule, most genes have been identified by defining a candidate gene by both its chromosomal location and its proprieties. Gene identification was based on methods in which the chromosomal location of the disease locus was not required (positional-independent strategies) and those that depended on this knowledge (positional cloning). In the former, gene identification was achieved based on thorough knowledge of the protein product, DNA sequence, or its normal function. In the latter, disease genes were identified using only knowledge of their approximate chromosomal location. Although both strategies are separate in principle, most commonly, geneticists and neuroscientists use a combination of both sets of information to identify a potential genetic variation. The most often used tool is based on NGS (as WGS and WES) and genome-wide association studies. There are some bioinformatics tools that help researchers to predict if a genomic variation could be damaged, but all variations should be tested with functional studies to ensure that they are related to a good candidate gene consistent with the disease phenotype.

In this context, the association between the presence of a certain mutation or mutations (genotype) and the resulting physical trait, abnormality, or pattern of abnormalities (phenotype) has been studied as a promising investigational tool. Several general principles have emerged as a result of the intensive study of causative variations in genetic disorders.

According to the Mendelian paradigm, a specific disease is caused by mutations in a single gene. Because there are 2 alternative forms of any given gene (alleles), a genetic disease can occur if a mutated allele was inherited from the father or from the mother (autosomal dominant transmission) or if both mutated alleles were inherited from the parents (autosomal recessive transmission). However, even single gene (monogenic) diseases can manifest with a wide range of symptoms, severity, and prognostic issues, which is called variable expressivity.

However, most neurologic disorders are complex (multifactorial) and not monogenic disorders. There are variations in the genome that are more frequent in the population (polymorphisms) and