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Pharmacogenetics, the Promise of Translating Personalized Medicine into Clinical Pediatrics

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Humans share the same genes but do not have identical DNA sequences. The latest 1000 genomes project reported over 84.4 million single nucleotide polymorphisms (SNPs), 3 million short insertions/deletions, and 60,000 structural variants in 2,504 subjects from 26 populations (1000 genomes project consortium 2015) (1). One of the most significant outcomes of identification of these differences is the development of personalized medicine.

The vision of personalized medicine is based on using an individual's genetic profile to guide decisions made regarding to the prevention, diagnosis, and make the best therapeutic. Pharmacogenetics, which also has been called individualized or precision medicine, has been widely recognized as a fundamental step toward development of personalized medicine. It deals with the influence of genetic variants on treatment response or the risk of serious adverse reactions to drugs. A great number of genetic variants are located in gene products that are involved in the metabolization, absorption, elimination and action of drugs. Single nucleotide variants as well as structural variants such as inversions and copy number variations (deletions and duplications) in these genes have been contributed to the drug response of individuals (2, 3). In the case of pediatrics, the impact of genetics on health and illness has been appreciated for many years. For instance, Down syndrome as a congenital disease was well known in the nineteenth century. Numerous other examples of disease with genetics implications, such as cystic fibrosis and Duchenne muscular dystrophy, having a significant impact on children's health, well-being and life expectancy have been known for many decades. However, most of these genetic disorders were historically either chromosomal polysomies (for example, Down Syndrome) or disorders that are inherited by classical Mendelian or X-linked inheritance (for example, cystic fibrosis or Duchenne muscular dystrophy). In contrast, majority of variants with pharmacological consequences are involved in remarkably more complex mechanisms and interactions of several genes and their products.

A growing number of studies are being published on the impact of individual genetic background on drug response. However, most of these reports have dealt with adult individuals and only a few studies have investigated the role of pharmacogenetics in pediatrics, with highlighting the importance of differences between children and adults. A major obstacle for such pediatric studies is that both ontogeny and genetic variation contribute to variability in therapeutic response across different age groups and developmental stages, which range through newborns, infants, children and adolescents (4-6). Pharmacogenetics research has been used in several fields of pediatrics, especially pediatric oncology, hematology, pulmonology, rheumatology, endocrinology, neurology, and gastroenterology. Following we shall present some examples of differences in drug response as a result of individual genetic background with a focus on pediatric pharmacogenomics.

Cancer is one of the commonest causes of death for children in developed countries. Given the fact that cancer treatment is a complex multi-criteria process and many of the disposition process of used drugs are likely to be subject to genetically determined variability, pediatric cancer seems to be an area of active pharmacogenetics research. For instance, the main therapy for acute lymphoblastic leukemia (ALL)- the most common type of cancer in pediatrics- (7) is 6-mercaptopurine (6-MP), a prodrug whose conversion to its active form depends on intracellular metabolism. Many metabolizing enzymes, in particular thiopurine methyltransferase (TPMT) and hypoxanthine phosphoribosyltransferase (HPRT) are involved in 6-MP disposition. The HPRT pathway leads to the active therapeutic metabolites of 6-MP, the 6-thioguanine nu-

cleotides (6-TGN) while TPMT competes with the formation of 6TGN, as it methylates 6MP to relatively nontoxic methylated metabolites, 6-methylmercaptopurine (6-MMP) and 6-methylmercaptopurine ribonucleotides (6-MMPR). The TPMT gene exhibits significant genetic polymorphisms with approximately 89% of the population having wild type TPMT, which is associated with normal TPMT enzyme activity, while 11% are heterozygous and have corresponding intermediate or low TPMT enzyme activity (4). Most importantly, 0.2 to 0.3 percent of the population is homozygous for mutations of TPMT and has low to absent enzyme activity. The three main TPMT alleles, namely TPMT *2, *3A and *3C, are known to account for 80% - 95% of the intermediate and low enzyme activity (5). Patients who are heterozygous at the TPMT locus are at intermediate risk of dose-limiting toxicity, but there is significant clinical variability due to other modifying factors. Results of multiple independent studies indicated a dose reduction by approximately 35% - 50% is required for these patients (6, 7). In patients with TPMT deficiency 6-MP is preferentially metabolized to produce high levels of 6-TGN; thus, treatments with standard doses of 6-MP is at significantly increased risk of myelosuppression, bleeding, infection, and death associated with increased levels of cytotoxic 6-TGN levels in the red blood cells and therefore requires a dose reduction of up to 90%. Noteworthy, TPMT activity is indicated to be higher in children than in adults when normalized for genotype, which needs to be accounted when assessing the TPMT phenotype.

Methotrexate (MTX), a structural analogue of folic acid, is an anti-folate chemotherapeutic drug in the treatment of ALL. Methylene tetrahydrofolate reductase (MTHFR) is an essential enzyme in the folate/ MTX metabolism pathway. Two MTHFR genetic variants have been found to modulate the efficacy and clinical toxicity of high doses of MTX (C677T and A1298C) in multiple studies (8). The variant TT genotype, associated with about 30% of wild-type (CC) activity, is present in about 10% to 12% of population. Heterozygotes CT genotype (about 60% activity) constitute approximately 40% of the population (9). A significant association of C677T polymorphism with overall MTX toxicity, hepatotoxicity, hematological toxicity, and neurotoxicity has been indicated (10).

Cisplatin is another widely used chemotherapy drug for the treatment of pediatric solid tumors. While a very useful chemotherapeutic agent, cisplatin produces many adverse events, one of the most serious being ototoxicity, with irreversible hearing loss. Single nucleotide polymorphisms in the drug-metabolism genes, thiopurine S-methyltransferase (TPMT) gene (rs12201199, rs1142345 and rs1800460) and catechol-O-methyltransferase (COMT) gene (rs9332377) have been found to be associated with cisplatin-induced hearing loss in children (11, 12). The suggested mechanism of ototoxicity is by the release and generation of both proapoptotic factors and free radicals within the sensory outer hair cells of the cochlea upon exposure to cisplatin (13). More than 90% of the children that carried at least one risk variant were shown to develop moderate-to-severe hearing loss in cisplatin treatment (11, 12). Therefore, testing for genetic variants associated with cisplatin-induced ototoxicity before the start of therapy could identify children at increased risk of hearing loss and enable personalized therapy.

One model of personalized medicine is the medical care for management of pediatric rhinitis and asthma (14). Current asthma treatments are based on long and short acting β2-adrenoreceptor (ADRB2) agonists (LABAs and SABAs), inhaled corticosteroids (ICS) and leukotriene antagonists. In the vast majority of patients, symptoms are well-controlled with these conventional asthma therapies. However, approximately 20% of patients are not responsive, a phenotype often called “difficult to treat” or severe asthma (15, 16). Different specific genes have been reported to predict response to these drugs.

Arg-16Gly polymorphism (rs1042713) in the ADRB2 gene have been contributed to drug response (17). Arg16Arg homozygotes and Gly16Arg heterozygotes were 5.3 times and 2.3 times more likely than Gly16Gly homozygotes to show a positive response to albuterol (an ADRB2 agonist), respectively (17). However, Arg16Arg carriers had a reduced response compared to Gly16Gly carriers when albuterol was used regularly (18). In case of severe asthma exacerbations, children with Gly16Gly showed a better response to albuterol (19). This observation has been replicated a number of times with different ADRB2 agonists but does not seem to hold for some LABAs, such as salmeterol (19). During regular therapy with LABA, reduced responses in Arg16Arg homozygotes have been reported in two small studies (20) but have not been found in several other larger studies (21).

Pharmacogenetics, an emerging field of science for identification of genetic variants that predict treatment response, is finding its way into pediatric practice. Pediatric pharmacogenetics has the potential to improve the personalization of medical treatment, enhancing the efficacy and safety of therapeutic agents in children. For a small number of drugs, genetic testing in children is now forming part of the guidance from drug regulatory agencies (22). However, as in many areas of medicine, clinical implementation in pharmacogenetics lag behind corresponding adult discovery and evidence-based recommendations for genotype-guided dosing in pediatric patients have not been well- established. Recognizing that “children are not small adults,” more highlights the spe-

cial considerations for medication use in children. Moving pediatric pharmacogenetics toward clinical implementation will require pediatric-specific evidence obtained from large cohort populations.

Footnote

Authors' Contribution: Mahsa Motavaf and Mansour Bahrami both were responsible for study concept and design and acquisition of data.

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