Translating pharmacogenetics and pharmacogenomics into drug development for clinical pediatrics and beyond

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Pharmacogenetic and pharmacogenomic investigations conducted in children must consider that human development from conception through to adolescence is a rapidly changing, dynamic process. An improved understanding of the gene networks that are involved in growth and development and of the unintended consequences of modulating those systems could provide insights into the susceptibility of an individual to drug-induced birth defects and to pediatric adverse drug reactions. Furthermore, these technologies potentially present the opportunity to develop novel, effective treatments for childhood diseases and for adult diseases that manifest primarily during childhood. The lack of pharmacogenetic and pharmacogenomic investigations in children and the potential to impact on all age groups provides a considerable incentive to invest in this area of research.

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▼ A series of legislative changes that were initiated in 1994 with the FDA (http://www.fda.gov) Pediatric Rule, as well as the explosion of genomic, transcriptomic and other –omic data in recent years, provide the basis for unique opportunities and challenges to improve the safety and efficacy of medications used to treat children. Some diseases that affect children, such as patent ductus arteriosus and Kawasaki's disease, have no adult correlates, whereas others [e.g. acute lymphocytic leukemia (ALL), neuroblastoma and Wilm's tumor) are rarely encountered, if at all, in adults. Furthermore, many diseases with complex etiologies that manifest during childhood [e.g. asthma, autism, attention deficit and hyperactivity disorder (ADHD), epilepsy and juvenile rheumatoid arthritis] persist into adulthood and often require chronic pharmacotherapeutic intervention. A better understanding of the genetic basis of age-specific disease processes and age-related variability in the response to medications used to treat these types of diseases should lead to improved drug treatment in patients of all ages, from pediatric through to geriatric. However, investigations directed at pediatric populations must also realize that human development from the prenatal period through to adolescence is a rapidly changing, dynamic process. Therefore, pharmacologic modulation of developing receptor systems and networks could have unanticipated and unintended consequences that do not become apparent or relevant until a later stage of the maturation process. For this reason, definitions of 'pharmacogenetics' and 'pharmacogenomics' must incorporate the added dimension presented by disease or treatment phenotypes that could potentially change throughout the developmental process. The purpose of this review is to highlight several situations that relate to the drug development process where the application of pharmacogenetic and pharmacogenomic strategies could improve pediatric pharmacotherapy.

What are pharmacogenetics and pharmacogenomics?

Pharmacogenetic studies investigate the affects of genetic factors on the inconsistency of drug response by assessing the extent of the contribution of variant forms of human genes to the observed variability in drug disposition, drug action or drug toxicity. The primary

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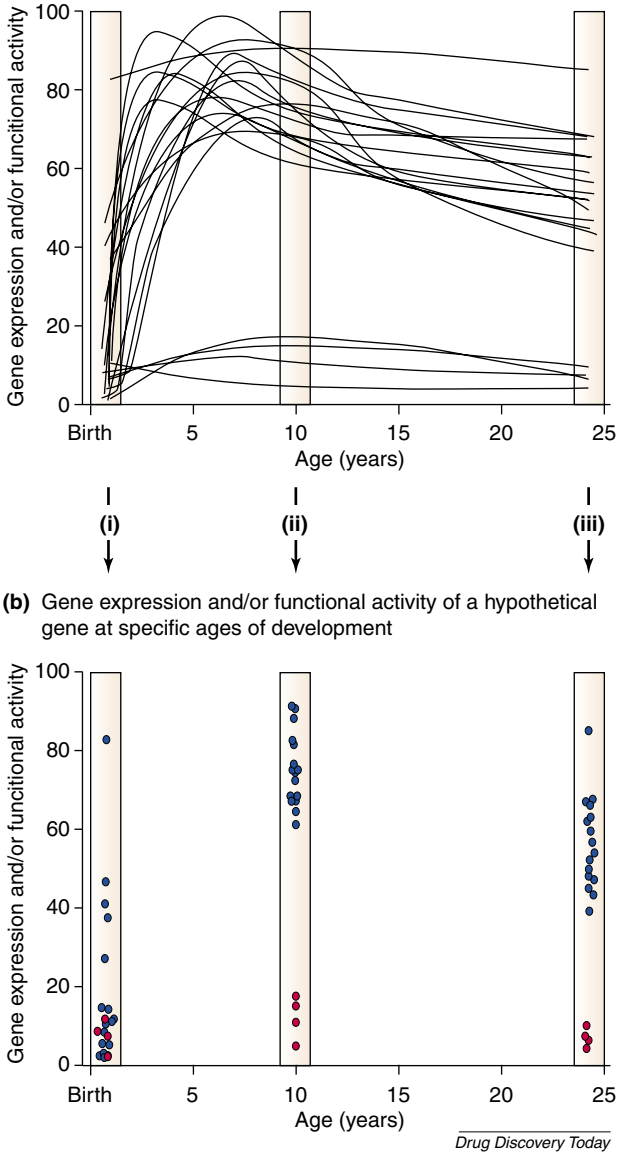

Figure 1. The role of developmental pharmacogenetics as a determinant of interindividual variability. **(a)** Developmental changes in gene expression and/or functional activity of a hypothetical gene for the first 25 years of life for 20 individuals. **(b)** Gene expression and/or functional activity at specific ages of development. In adults **(iii)**, allelic variation within the coding region of the gene gives rise to two distinct phenotypes, high activity in 92% of the population (blue circles) and low activity in 8% of the population (red circles). However, there is interindividual variability in the rate at which functional activity is acquired postnatally such that the two phenotypes are not readily distinguishable shortly after birth **(i)**. In addition, there might be discrete developmental stages during which the gene expression or activity appears greater than that observed in adults **(ii)**. Developmental pharmacogenomics involves characterizing the variability in expression of all genes in a pathway or network throughout growth and development.

goal of pharmacogenetics is to identify the right dose of the right drug for a given individual. Typically, genotyping or phenotyping strategies focus on a single gene (e.g. CYP2D6 pharmacogenetics). Pharmacogenomic investigations use constantly emerging and evolving genomic technologies to encompass comprehensive, genome-wide strategies targeted at identifying all factors that influence the response of a patient to small molecules that have been administered with therapeutic intent. Although many different definitions for 'pharmacogenomics' have been presented in the literature, from a drug development perspective, pharmacogenomics is best described as identifying (developing) the right drug for a given disease in the context of complex genomic factors.

Application of pharmacogenetic and pharmacogenomic approaches to the treatment of pediatric diseases requires an appreciation of the dynamic changes in gene expression that accompany maturation from embryo through fetal development, the neonatal period, infancy, childhood and adolescence. It can be readily appreciated that individual gene expression does not occur in isolation during development but is instead an integral component of larger, complex networks of genes that interact during, for example, organogenesis, the establishment of receptor systems and neural networks, drug biotransformation activities and the acquisition of immune functions. In other words, the patterns of gene expression and the nature of the gene interactions that contribute to the pathogenesis of pediatric diseases (thereby serving as potential targets for pharmacologic intervention) might only be discernable or relevant at specific, crucial points in the developmental continuum. Thus, defining 'pharmacogenomics' as the study of how interacting systems of genes determine drug response [1] is particularly appealing in a pediatric and developmental context because this definition captures the essence of the developmental processes that characterize maturation from the time of birth through to adulthood while retaining a focus on the individual.

Application of developmental pharmacogenomics to drug discovery

Undoubtedly, there are several areas in which developmental pharmacogenetic and pharmacogenomic strategies can be applied to improve the use of currently marketed drugs or to optimize the development of new therapeutic entities intended for use in adult and pediatric populations. In this context, it is important to distinguish between the pharmacogenetics and pharmacogenomics of development and of interindividual variation. The scenario presented in Figure 1 (for a hypothetical gene) illustrates how the pharmacogenetic polymorphism of a gene could result

in the presence of distinct phenotypes in adults (i.e. extensive and poor metabolizers) that characterize the interindividual variability of that gene product in the population. However, this degree of interindividual variation might not be apparent in neonates or infants because of the developmental delay in the acquisition of that particular activity. Therefore, the pharmacogenetics of development seeks to characterize the genetic basis of the change in phenotype that occurs in a given individual throughout maturation, with the potential for the occurrence of distinct developmental profiles in the population. The pharmacogenomics of development takes into consideration that the level of expression of networks of genes, rather than individual genes, varies as children mature and thus contributes to interindividual variability in drug response. The remainder of this review will address four broad applications of pharmacogenetics and pharmacogenomics that are relevant to the safe and effective use of medications in clinical pediatrics.

Drug-induced birth defects

In susceptible individuals, the exposure of an unborn fetus to medications administered to the mother during pregnancy might lead to several undesired consequences, including *in utero* death, growth retardation and malformation or functional abnormalities in the developing fetus [2,3]. Whereas most events classified as major malformations are readily apparent or manifest relatively soon after birth, less evident adverse consequences of perinatal drug exposure might not be revealed until some time later in life. For example, Poirier *et al.* [4] reported recently that mitochondrial DNA content was reduced in infants born to HIV-positive mothers treated with zidovudine during pregnancy compared to infants born to untreated HIV-positive mothers (although mitochondrial DNA content was significantly lower in both groups compared to infants born to untreated HIV-negative mothers). Furthermore, this result was also observed in mitochondrial DNA samples obtained at two years of age [4]. Results from a follow-up study of HIV-negative children born to HIV-positive mothers suggested that children exposed to antiretrovirals during pregnancy could be at an increased risk of developing neurological symptoms consistent with mitochondrial dysfunction [5]. Specifically, the 18-month incidence of neuro-mitochondrial disease was observed to be 0.26% in exposed children compared to a general estimate of 0.01% for the population at large, which implies that the toxic effects in susceptible individuals persist well beyond the period of systemic exposure. Although these results need to be supported by data from prospective, longitudinal studies that address specific endpoints of neurological function, existing data illustrate the need for longer-term perspectives when addressing the undesired consequences of drug exposure in developing fetuses.

It is important to note that although epidemiological data suggest that exposure to a particular xenobiotic during pregnancy is associated with an increased risk of a particular malformation or longer term sequelae, a fundamental link between the two events is more difficult to establish. Furthermore, it is clear that in a given exposed population there are a small number of individuals who are at extremely high risk of manifesting the associated malformation and/or adverse consequence, whereas the majority are at considerably lower risk or even unaffected by the exposure. The ability to identify individuals or groups that have an increased risk of developing these undesired events would be a significant advance, particularly when exposure cannot be avoided or when it might not be in the best interest of the mother and/or fetus to discontinue medication (e.g. treatment of epilepsy, severe asthma or HIV infection). The challenges of developmental pharmacogenomics are to identify all components of the network(s) that are involved in the various aspects of normal human embryonic and fetal development, and to characterize the role of allelic variation in those components that leads to the dysregulation of gene expression or gene product dysfunction and subsequent adverse fetal and/or neonatal maturation in response to perinatal drug exposure. One caveat is that different networks of genes are operative at various stages of development and the developmental acquisition of additional processes, such as drug biotransformation and transport, protein and DNA repair and apoptotic and tissue remodeling pathways, can be expected to exhibit some degree of variability across a population. As crucial as this information would be to pharmaceutical companies seeking to minimize the teratogenic potential of compounds under development, global gene expression and proteomic investigations of human prenatal development require, on a population basis, access to tissues from a large number of subjects. Furthermore, the samples must be of sufficient viability to enable isolation of intact mRNA and protein of interest. In addition to the logistical hurdles associated with their acquisition, the use of these tissues is not without considerable moral, ethical and political controversies [6].

Adverse drug reactions

Based on available *in vitro* data and *in vivo* pediatric pharmacokinetic studies, drug clearance pathways appear to undergo dramatic changes throughout the maturation process. The activities of many enzymes that are involved in drug biotransformation are absent or limited at birth

[7–9]. This raises the possibility that there might be periods of increased vulnerability to concentration-dependent drug toxicity until such a time as the pathway(s) involved in drug clearance become functional; a classical example of this phenomenon is the cardiovascular collapse associated with delayed maturation of chloramphenicol glucuronidation. Recent reports of apparent serotonin-selective reuptake inhibitor (SSRI)-related toxicity in neonates exposed to paroxetine, fluoxetine and sertraline during the third trimester of pregnancy [10] underscore the value of 'developmental pharmacogenetics' (Figure 1) in the characterization of population variability and in the determination of the rate at which important drug biotransformation pathways [e.g. cytochrome P450 (CYP) 2D6 and CYP3A4] are acquired postnatally. Data acquired from a prospective study [11] implicate, somewhat controversially [12], a hyperserotonergic mechanism in affected infants, which is consistent with the delayed acquisition of functional drug biotransformation activity.

Some severe idiosyncratic adverse drug reactions (ADRs), such as the risk of developing Reye's syndrome on taking aspirin [13], valproic acid (VPA) hepatotoxicity [14] and the cutaneous toxicity associated with lamotrigine [15,16], occur more frequently in children than in adults. The mechanisms by which these toxic effects are induced are poorly understood and, therefore, as yet there are no explanations for the apparent increased risk of these events occurring in children. Pharmacokinetic and therapeutic drug monitoring data obtained *in vivo* imply that after infancy some drug biotransformation pathways exceed the capacity of the corresponding pathways in adults, when dosage requirements and/or drug clearance between children and adults are compared and normalized to body weight [17]. However, this apparent increased drug biotransformation capacity in children compared to adults could be an artifact of normalizing drug clearance for body weight. Although this issue is far from resolved [18], it has been proposed that increased CYP activities (e.g. CYP1A2 and CYP3A4) during childhood could result in increased formation of reactive, potentially toxic metabolites. If an increase in bioactivation is not accompanied by a corresponding increase in detoxification capacity, or if these pathways are not fully developed (particularly those involving glutathione synthesis and conjugation), a net increase in the concentration of the reactive metabolites formed in the body could represent a significant determinant of risk for the development of idiosyncratic ADRs in young children. At present, few (if any) data characterizing the ontogeny of drug bioactivation are available. Furthermore, rather than focusing on the ontogeny of individual drug biotransformation enzymes, future developmental pharmacogenetic and pharmacogenomics studies should address whether or not developmental changes are associated with an imbalance in bioactivation and detoxification mechanisms, and whether or not such an imbalance contributes to periods of increased susceptibility for children of particular ages or developmental stages (i.e. increased risk of valproate hepatotoxicity in children less than two years of age). Such studies could be integrated into protocols for monitoring children that are receiving 'drugs of concern' as part of their prescribed pharmacotherapeutic regimens.

Finally, because the life expectancy of children is greater than that of adults, drug exposures or chronic treatment that is initiated during childhood, before maturation is complete, might have consequences that do not become apparent until later in life. For example, children who have defective thiopurine S-methyltransferase activity and are being treated with 6-mercaptopurine for ALL have a significantly increased risk of developing secondary malignancies such as irradiation-induced cranial tumors [19] and etoposide-induced acute myeloid leukemias [20]. Short-term use of granulocyte colony-stimulating factor has also been associated with an increased risk of therapy-related myeloid leukemia or myelodysplasia [21]. A pharmacogenomic strategy implementing expression profiling of diagnostic ALL bone marrow samples suggests that it could be possible to identify patients at risk of developing secondary acute myeloid leukemia, at least in a subset of ALL patients [22]. In the future, analogous approaches might be applied to resolve current controversies, such as the possibility that inhaled corticosteroids impair linear growth in children [23], in addition to other long-term, unintended consequences of drug treatment in young children.

Pharmacogenomics of drug response and new therapeutic targets for pediatric disease

Pharmacogenomics could aid in the functional characterization of diseases and disease processes that are either uniquely pediatric or are nominally 'adult diseases' that also occur in children. This characterization is particularly relevant to those situations where disease 'phenotypes' might change with growth and development (i.e. different 'wheezing' phenotypes in infancy [24]). It is not reasonable to expect that adult disease treatment paradigms can be meaningfully applied to conditions that affect newborn infants [e.g. patent ductus arteriosus and persistent pulmonary hypertension of the newborn (PPHN)] or childhood diseases (e.g. Kawasaki's disease, ALL, Wilm's tumor and neuroblastoma) that are rarely encountered in adults. Indeed, at present, the best example of the potential for genomic technologies to impact on the treatment of pediatric

disease can be found in the area of pediatric oncology and, specifically, in the treatment of ALL. Recent findings suggest that gene expression profiling could provide a robust alternative to the immunophenotyping, cytogenetic and molecular diagnostic analyses that are currently used to assign ALL patients to specific risk groups [22]. Furthermore, expression profiling has demonstrated that, within individual leukemia subtypes, distinct gene expression patterns are apparent in diagnostic blasts from patients who remain in complete continuous remission, who develop a hematologic relapse or secondary acute myelogenous leukemias and samples obtained at the time of ALL relapse. These findings indicate that this tool has the potential to identify patients at a high-risk of treatment failure [22]. A recent analysis of acute treatment-induced changes in the gene response of ALL blasts obtained one day after initiation of treatment with mercaptopurine alone, high-dose methotrexate alone or equivalent doses of mercaptopurine in combination with either high-dose or low-dose methotrexate revealed several new, important insights into the cellular response to these treatments [25]. For example, changes in gene expression were treatment-specific and could accurately discriminate among the four treatments. In addition, ALL cells of different molecular subtypes shared common cellular responses to treatment suggesting that it could be possible to personalize treatment strategies in ALL. As well as the obvious benefits of accurate diagnosis and prediction of treatment response to existing treatment options, perhaps the most exciting aspect of gene expression studies is the possibility that the data obtained can be used to assemble signal transduction pathways and develop novel chemotherapeutic regimens.

Pharmacogenomic approaches might also lead to a better understanding of age-dependent responses to prescribed medications. Our knowledge of how receptors and signal transduction pathways change through growth and development is minimal, but clearly this is a key element of recognizing whether or not therapeutic benefit can be expected in children treated with compounds initially developed to treat adult conditions. For example, will serotonin- or norepinephrine-selective reuptake inhibitors be uniformly effective in children of different ages or developmental stages diagnosed with ADHD if expression of the reuptake pumps is relatively low or considerably higher in one stage compared to another? Understanding the consequences of therapeutically modulating receptor and signal transduction systems during periods of maturation and development is becoming increasingly important because accumulating experience is beginning to reveal, for example, the difficulty in demonstrating the efficacy of using the same antidepressants in children that are used successfully in adults, and the possibility of distinct toxicity risks associated with their use in children and adolescents relative to adults. As an example of the concerns associated with toxicity risks, the UK Department of Health (http://www.dh.gov.uk) and the FDA recently issued cautionary statements regarding the use of SSRIs in pediatric patients suffering from major depressive disorder. Specifically, concern was raised regarding a possible correlation between SSRI-therapy and an increased risk of self-harm and/or potentially suicidal behavior in children and teenagers less than 18 years of age undergoing treatment with these agents. Although the FDA has not yet completed its review of the data and presented its conclusions, it emphasized two points in a recent release (http://www.fda.gov/cder/drug/advisory/mdd.htm). First, of the seven drugs evaluated in pediatric major depressive disorder under the pediatric exclusivity provision (citalopram, fluoxetine, mirtazepine, nefazodone, paroxetine, sertraline and velafaxine), the FDA has been unable to rule out an increased risk of suicidal thoughts for any of the compounds. Second, data reviewed were adequate to show efficacy only for fluoxetine. This situation raises several important issues with respect to the extrapolation of safety and efficacy data derived from adult studies to children. For example, it is difficult to know whether the symptoms of suicidality represent unintended consequences of pharmacologic modulation of maturing neurochemical networks (receptor-signal transduction pathways) that occur as the brain develops, or whether the symptoms represent developmental differences in the nature of depressive illness between children (and adolescents) and adults [26].

Although advances in the treatment of ALL generate optimism that genomic approaches, such as gene expression profiling, might improve the management of other diseases of childhood, this optimism is tempered by several logistical and practical considerations. Considering ALL, leukemic blasts are relatively accessible cells. However, for many other diseases and conditions that either manifest during childhood or affect children (e.g. asthma, epilepsy and pervasive developmental disorders), the relevant tissues might not be readily available, nor is it necessarily possible to obtain samples at the most informative time point (i.e. during an actual seizure episode). Thus, acquiring sufficient numbers of samples to address pharmacogenomics issues on a population basis is a further challenge. Creative solutions will be necessary to solve these real problems.

Pharmacogenomics for clinical pediatrics and beyond

Is it possible that the results of pharmacogenomic studies conducted in fetal or postnatal age groups could be applied

to the treatment of diseases in adults? The answer to this rhetorical question could lie in the results of studies investigating the intriguing but controversial 'thrifty phenotype and genotype' or, more generally, 'fetal origin of adult disease' hypotheses. The 'thrifty genotype' hypothesis originally proposed that the fuel conservation properties of otherwise lethal 'diabetogenic genes' conferred a selective advantage under conditions of subsistence living but became detrimental under conditions of over-nutrition, leading to the high incidence of type 2 diabetes in affluent societies [27]. An extension of this hypothesis is the 'thrifty phenotype' whereby poor fetal nutrition results in 'thrift' that requires adaptive changes in the developing fetus to conserve energy resources, ultimately manifesting as intrauterine growth retardation and impaired development of specific tissues [28]. The broader 'fetal origins of adult disease' hypothesis proposes that a predisposition to cardiovascular, metabolic and endocrine diseases later in life is a function of imprinted adaptive responses to intrauterine stressors (altered nutritional or endocrine status, hypoxia or maternal infection) that might be beneficial for short-term survival but detrimental in post-reproductive years [29]. Although initially greeted with skepticism, more rigorous application of epidemiological principles has resulted in the publication of data supporting a relationship between fetal and postnatal life that contributes to the risk of disease later in life [30,31].

An examination of the validity of the thrifty phenotype hypothesis is certainly beyond the scope of this review. However, it is important to note that the same general principles are being applied to other situations where exogenous influences during pregnancy are associated with adult disease, for example, second trimester influenza epidemic and schizophrenia [32], prenatal glucocorticoid administration and hypertension [33,34] and exaggerated increases in pulmonary artery pressure following hypoxic challenge in adults that had neonatal pulmonary hypertension as infants [35]. The general underlying theme appears to be that disturbances in the intrauterine environment trigger adaptive changes that modify fetal development and, subsequently, alter the risk of future adverse consequences. Investigations targeted at identifying and understanding the affected gene networks could ultimately lead to uncovering relationships between allelic variation in the affected genes and the long-term risk of disease. For example, it is probable that affected individuals will respond in different ways and to varying degrees. Some individuals might be able to deal with minor day-to-day changes in environment but might not be able to respond appropriately, because of genetic variations, to sustained (nutritional deficiencies or chromic infection) insults or to acute, overwhelming (maternal drug or environmental toxicant exposure during pregnancy) insults. The point is that investment in fetal or developmental pharmacogenomics could have the potential to pay enormous dividends in adult or geriatric medicine

Summary and conclusions

Analogous to the majority of other papers that review the future promise of pharmacogenomics [36], the perspective presented here also probably paints a picture of unrealistically high expectations. There are certainly many opportunities for the application of pharmacogenomic strategies to have a favorable impact on the safety and efficacy of existing medications and on the development of new therapeutic entities for the treatment of disease in children. Furthermore, there is the argument that adult and geriatric medicine could also benefit from research in this area. Nevertheless, there are several daunting challenges to be overcome, not least of which is accessibility to high-quality tissues and other biological samples (i.e. for expression profiling studies) at the appropriate stages of development. Genetic association studies show promise for determining the relationship between allelic variation and drug response in children, as has been reported between β_2-adrenoceptor variants and albuterol response in asthmatic children [37], and to identify new therapeutic targets, as has been described for autism [38]. However, for many complex pediatric diseases (e.g. asthma, autism and epilepsy), the developmental stage that is crucial for the pathogenesis of the disease remains unknown, and identification of this stage will require successful integration of epidemiologic, genomic and related (i.e. proteomic, transcriptomic and metabolomic) strategies. Large-scale systematic endeavors, such as the recently proposed Human Phenome Project [39], could provide the data resources necessary to address these challenges. The relative paucity of pharmacogenetic and pharmacogenomic investigations in children compared to adults and the potential to impact on the entire age continuum provides a considerable incentive to invest in pharmacogenomics.

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