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## Genomic Sciences for Developmentalists: A Merge of Science and Practice

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### Abstract

*The etiological forces of development have been a central question for the developmental sciences (however defined) since their crystallization as a distinct branch of scientific inquiry. Although the history of these sciences contains examples of extreme positions capitalizing on either the predominance of the genome (i.e., the accumulation of genetic factors driving development) or the environmentome (i.e., the accumulation of environmental factors driving development), the moderate view of development as the emergence of a person from a particular genome and within a specific context has settled into the driver's seat and is disputed no longer. Yet, although there is a converging theoretical perspective, a gap between this perspective and practice remains. In other words, society needs to translate this position into praxis. This opinion exemplifies the current state of corresponding knowledge in the developmental sciences, with a particular emphasis on the understanding of the role of the genome in child and adolescent development, and offers a set of comments on how this translation is being shaped by the newest technologies in the genomic sciences. © 2015 Wiley Periodicals, Inc.*

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The developmental sciences have, by definition, been attentive to the question of the etiology of human development in general and child and adolescent development in particular. Although specific answers to this question have been determined, chiefly, by philosophical–psychological theories and the availability of particular research methods, developmentalists have continued to ask this question, rephrasing it as theories of development and methods to study it have multiplied in number and sophistication. By definition, then, the etiology question could not remain dormant in the outburst of relevant knowledge generated by the completion of the Human Genome Project and subsequent wave of technological and methodological advances. The complexities of translating these advances into the domain of public health for either prevention or health management are still not well understood, nor mastered in the general and developmental sciences in particular. In this opinion piece, only four junctions of genomic and developmental sciences (prenatal genetic testing, newborn genetic testing, diagnosis of complex disorders, and tracking of the epigenome throughout development) are sampled to exemplify these complexities and outline the relevant lines of inquiries that are likely to soon originate in the context of research into child and adolescent development.

### **Prenatal Genetic Testing**

Previously limited primarily to high-risk pregnancies, prenatal genetic testing has recently changed its potential as the technology has developed to incorporate two innovations (Hui, 2013). The first pertains to the utilization of cell-free fetal nucleic acids (cffNA, i.e., both fetal DNA and RNA), which originate primarily from trophoblasts (the layers of cells that surround an embryo and attach it to the uterus), then enter maternal circulation after crossing the placenta at quantities large enough to become detectable from about 7 weeks of gestation, and comprise up to 10% of the total maternal cell-free DNA. The second pertains to the development of the technologies that allow using next-generation sequencing with cffNA. These two innovations have resulted in the development of noninvasive prenatal diagnostic (NIPD) tests that have been rapidly gaining popularity. The first commercial tests became available only in 2011 and were limited to the diagnoses of three aneuploidies—Down (trisomy 21), Edwards (trisomy 18), and Patau (trisomy 13). Since then, the technology has been improving, and, although different commercial providers offer different services, the repertoire of the test has now grown including microdeletions and the detection of specific mutations (Sequenom, 2014). NIPD can be performed at early stages of pregnancy, does not pose physical risk to the fetus, and is minimally associated with maternal distress. There are companies (e.g., Sequenom, Verinata, Ariosa, Natera) developing NIPD tests with direct-to-consumer

potential. Thus, in the second quarter of 2014, Sequenom reported approximately 40,800 accessioned patient samples for the company's prenatal test MaterniT21, more than 7% over the prior year's last quarter and 3% over the first quarter of 2014. Although there do not appear to be any published data yet on the impact of the results of NIPD on pregnancy-related decision making, there are rising concerns (Allison, 2013) pertaining to NIPD's widespread availability, its capacity to provide comprehensive whole-genome coverage, relative lack of quality control and administration and interpretation regulation, and the potential for encouraging discrimination against those with genome syndromes (first, causing increased termination rates of fetuses identified with certain genomic syndromes and, second, de-incentivizing the development of treatments for existing or future patients with these syndromes). It is important to instigate specific lines of inquiry into all aspects of pregnancy-related decision making, as it pertains to the formation of the next generation of children and the representation of children with special needs among them.

### **Newborn Genetic Testing**

Although having celebrated its 50th anniversary in the United States in 2013, irrespective of its "age" and reputation as one of the most successful public health programs of the 21st century (CDC, 2011), the horizons of newborn genetic screening have also been transformed under the pressure of new technologies. The program, although as controversial now as at its inception, identifies annually ~12,500 newborns with specific heritable disorders mandated by health authorities for identification; these disorders cause ruinous effects if not diagnosed and treated prior to symptom manifestation. Yet, even though this program is appraised as having inestimable value to children and families, for whom devastating manifestations have been prevented due to the early diagnoses, it is still fraught with controversy (Lewis, 2014). Today's controversy pertains to the utilization of the sequencing data from newborn testing. The field has high expectations regarding the findings and recommendations that will be generated within the framework of the Genomic Sequencing and Newborn Screening Disorders (GSNSD) program, initiated by the U.S. government in 2013 (Kaiser, 2013). One of the charges of the program is to educate the public about the superiority of sequencing information over the data that have been gathered for years by conventional newborn screening methods, and their usefulness for families and practitioners in preventing, treating, and maintaining inherited conditions. Depending on the findings and observations generated in the context of this program, it is possible that whole-genome-based tests will not replace what is currently known as newborn genetic screening. Yet, as in the case of prenatal screening, the market has offered commercial alternatives that are completely within reach of upper-middle class and wealthy

families. Thus, using either direct-to-consumer or obligatory testing, a significant portion of parents will get such data. Therefore, the system needs to prepare for situations when both pediatrician and other health professionals will face educated parents armed with the genomic sequences of their children and arguing for particular decisions, placements, and accommodations. The GSNSD program is an attempt to at least start the relevant discussions, if not provide solutions.

## **Diagnosis of Complex Disorders**

Irrespective of both the spectacular successes and disappointing lack of progress, the major premise behind genetic and genomic research pertains to its capacity to be used as a diagnostic tool (Korf, 2013). This tool is especially important in the developmental sciences, as the majority of childhood and adolescent conditions, although heritable, do not onset early in life, opening a particularly important window of opportunity for prevention and intervention. There is hope that, as with Mendelian disorders diagnosed by newborn tests, individual risk for complex disorders may also be detected early in life, so that their manifestation may be ameliorated or prevented. Today the premise for genetic/genomic diagnoses for complex behavior disorders is exemplified by the data-armed discussion of three possibilities: whether the genetic contribution to so-called common (i.e., with the prevalence of  $>1\%$ ) conditions may be captured as (a) a combination of a large number of specific common alleles, each of which might be characterized by a small effect; (b) an impact of a specific rare allele with a large effect (i.e., one of many alleles whose frequency in the general population is  $<1\%$ ); or (c) a co-occurrence of some risk alleles and some risk environments (Gibson, 2012). Methodologically, these possibilities can be predominantly aligned with different technologies where the investigation of common variants can be carried out by either a genome-wide association study (GWAS, where only known polymorphisms are analyzed) or genome sequencing (where all polymorphisms, known and unknown, can be registered), but the investigation of rare variants requires sequencing. Similarly, if the disease model assumes the dominance of genetic causes, then either GWAS or sequencing can generate relevant data, whereas the presence of some environmental risk factors in the etiological model calls for the investigation of the environment. Although each of these methodologies has its strengths and weaknesses related to effectiveness, ease of implementation, and cost (Koboldt, Steinberg, Larson, Wilson, & Mardis, 2013), collectively they have generated enough data to illustrate what developmental psychopathology has referred to as equifinality (Cicchetti & Rogosch, 1996). In other words, what are currently known as complex developmental disorders (e.g., autism spectrum disorders, attention-deficit hyperactivity disorders, and learning and language disabilities) might well have examples of relevance in all three models mentioned earlier to the emergence of these

disorders. As the workings of the genome are being cataloged with unprecedented force, the diagnoses of common disorders caused by both common and rare genetic variants will be increasingly incorporated into the day-to-day practice of developmentalists. Opinions in the literature state that someday, whether prenatally, at birth, or at school entrance, everyone will have their genome sequenced. Yet, although technological feasibility and associated costs do not appear to be major obstacles anymore, the developmental significance of such data is far from understood and, thus, needs to be carefully investigated.

### **Tracking the Epigenome Throughout the Development**

Given the pattern of today's geopolitical and political events, it is profoundly sad that centuries of civilization have not eliminated childhood adversity; on the contrary, its typology seems to have widened, deepened, and diversified. Whether it is in Muslim Gaza or Christian South-Eastern Ukraine, Qatar with a GDP per capita of \$91,379 or the Democratic Republic of Congo with GDP per capita of \$231, democratic USA or the conservative Kingdom of Saudi Arabia, children encounter adverse living conditions caused by natural and human-made disasters (Al-Mahroos & Al-Amer, 2012; Stoltenborgh, Bakermans-Kranenburg, & van Ijzendoorn, 2013; Tol, Song, & Jordans, 2013; Yonekura, Ueno, & Iwanaka, 2013). Remarkably, although children may experience the same type and quantity of adversity, the child-based aftermath is distributed continuously, ranging from healthy adjustment with high resilience to severe maladjustment with challenged mental and physical health across the lifespan. The mechanisms behind this continuity are realized to be complex and shaped by the interconnectivity of influences between the properties of the genome, its epigenetic superstructure, the stress-related hormonal machinery, the immune system of the child, and many other factors. Typically, maladjustment arises from an unfavorable combination of all these components—for example, a dysregulated (i.e., challenged by the presence of multiple risk variants) genome, low levels of cortisol in the stress-response system, and elevated markers of inflammation in the immune system. Substantially less is known about the epigenome and which of its facets should be viewed as risk versus protective factors of its functioning. Epigenetic mechanisms encompass functional changes in genes without altering the DNA sequence itself (Rivera & Ren, 2013); they are control mechanisms impacting both gene regulation and gene transcription (and, therefore, expression). The major appeal for studies of epigenetic mechanisms in the context of child and adolescent development is that they are potentially reversible. These mechanisms are multiple, with the best studied today being DNA methylation (which results in a decrease, silencing, or increase of gene expression by hyper- or demethylation), histone modification, and aberrant expression of micro-RNA. To illustrate, there is a growing body of literature connecting changes in

patterns of methylation to subsequent developmental outcomes, exemplified by the connections between maternal famine at periconception during the Dutch Hunger Winter (1944/45) and their offspring's demethylation of an insulin-like growth factor II (IGF2) in adulthood, at 60+ years of age (Heijmans et al., 2008); between maternal depression and anxiety in late pregnancy and offspring's hypermethylation of the glucocorticoid receptor (GR, also known as NR3C1—nuclear receptor subfamily 3, group C, member 1) gene from umbilical cord blood samples and elevated cortisol stress reactivity at the age of three months (Oberlander et al., 2008); and between physical maltreatment and greater methylation within exon 1F in the NR3C1 (Romens, McDonald, Svaren, & Pollak, 2014). In addition to studies that target specific physiological pathways and corresponding gene candidates, there is also an increasing mass of research on genome-wide changes in the patterns of methylation in children who have experienced a specific type of adversity compared with children who have not experienced the same adversity. Thus, statistically significant group differences have been registered in the methylomes of children who lost their parents early and were growing up in orphanages (Naumova et al., 2012), of adults with and without the experience of foster care as children (Bick et al., 2012), and of maltreated children and controls (Yang et al., 2013). There are also examples of studies where indicators of parenting have been reported to be associated with delayed whole-genome methylation patterns in the offspring (Essex et al., 2013; Naumova et al., in press). Thus, embedding epigenetic ideas into developmental science research has been progressing very quickly, yet, as is always the case in new research fields, many more and, when possible, prospective studies will clarify, qualify, and quantify the role of epigenetic mechanisms in development.

## Concluding Remarks

Clearly, both technological and conceptual developments in the genomic sciences have had an incredible impact on the knowledge of human development, in just a very short time. Although there are ongoing attempts, both in the private and public sectors, to convert this knowledge into everyday practice from preconception through childhood and adolescence, the success of such conversion is contingent on the adequate resolution of a variety of challenges. Among these challenges are practical (e.g., the manipulation—acquisition, storage, and analyses of big data, generated by whole-genome technologies; data de-identification and/or privacy; differentiation of clinical and research usage of data) and ethical (e.g., legal and temporal limits of parental informed consent; interpretational scope acceptable for whole-genome data; practitioners' and patients' ignorance pertaining to functional vs. silent, neutral vs. pathological consequences, and probabilistic vs. deterministic impacts of variation in the human genome). Although overcoming the practical challenges appears to be only a matter

of time with the development of proper technical solutions, ethical challenges might overshadow the advantages to both individuals and societies. Both practical and ethical challenges have and will generate new questions and new directions of research, pertaining to what, if, and how genomic science might change the landscape of the developing sciences. This opinion has highlighted a few possible directions of research, but, likely, even more will originate at the junction of genomic sciences and child and adolescent development.

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