CHILDREN'S MENTAL HEALTH TASK FORCE

GENETICS FOCUS GROUP

Over the past ten months, the Task Force's Genetics Focus Group has gathered and exchanged reference materials relating to genetic contributions to the entire spectrum of mental disorders in children with particular attention to the three broad disorders/conditions selected for in-depth focus by the Task Force at its November 6, 2013 meeting – Attention Deficit Hyperactivity Disorder (ADHD), Mood Disorders and Conduct Disorders. We reviewed material in a standard child psychiatry test, Essentials of Lewis's Child and Adolescent Psychiatry by Yale Child Study Center professors Fred Volkmar and Andres Martin, published in 2011, current literature – in particular recent reviews – relating to the three highlighted disorders but also in other mental health disorders such as autism spectrum disorders and recent literature on advances in genetic testing including DNA microarrays, whole-exome and whole-genome sequencing. We considered both the genetics associated with specific diseases/disorders as well as the genetic and epigenetic associations with parental child raising and various environmental factors popularized under the rubric "Lifecourse Health Development". Dr. Genel also met with various experts at the Yale Child Study Center and Department of Pediatrics including Drs. Fred Volkmar, Joseph Woolston and Abha Gupta. Dr. Gupta provided a well received "Overview of Genetics of Behavioral Disorders in Children" concentrating on her field of scientific interest, Autism Spectrum Disorders(ASD), at the Task Force's May 21, 2014 meeting.

With respect to the three specific disorders selected by the Task Force, it has been long recognized that there are strong familial associations although specific genetic etiologies in a traditional gene-clinical disorder model have for the most part been limited to specific disorders such as in Rett Syndrome and MECP2 mutations and Fragile X Syndrome and FMR1 mutations in ASD, as described by Dr. Gupta. Specific genes have been identified which convey increased risk in more well defined mental health disorders such as bipolar 1, but the clinical heterogeneity of the disorders selected by the Task Force, the host of mental health disorders in general and their clinical overlap make genetic cause and effect associations unreliable except in well defined genetic disorders or in specific families. In all of these clinically defined disorders it is postulated that the genetic liability instead reflects the collective action/interaction of many genes of individual small effect rather than the effect of any specific genetic mutation/variation.

Among the three disorders selected, ADHD is one of the more common with an estimated 8-12% worldwide incidence and has one of the highest heritability, estimated to approach 75% in twin studies with significantly higher concordance in monozygotic than in dizygotic twin pairs (Goldman, Genel et al, 1998). While a number of specific genes have been reported, none meet a rigid significance threshold for genome-wide association. In addition there is frequent clinical overlap with affective/mood disorders, childhood conduct disorder, personality disorders and substance abuse. ADHD is particularly associated with conduct disorders (~50% of cases per Volkmar & Martin), anxiety disorders (~25-30%) and mood disorders, especially in older children. A overview editorial in a symposium issue of the American Journal of Medical Genetics concludes that the advent of whole exome and whole genome sequencing "promise to provide further understanding of the likely genetic architecture of ADHD, how large these effects can possibly be, and the extent to which heterogeneity is inhibiting our capacity to understand ADHD at a neurobiological level". (Neale & Faraone, 2008)

Among the entities generally classified under the broad category of "mood disorders", depressive disorders and classic bipolar illness have very strong hereditary features, although distinct separation is often difficult in

childhood and a precise diagnosis per standard criteria may be difficult (Volkmar & Martin). Much as in ADHD, depressive disorders have significant concordance of ~ 40-65% in twins, higher in identical twins. There are also strong environmental factors, including economic adversity, neglect & abuse, loss of a parent or primary caretaker. Classic bipolar illness is highly inheritable, estimated to account for 60-85% of variance in risk but the clinical diagnosis of mania, particularly in pre-adolescent children, is "complex and controversial" (Volkmar & Martin). A recent review concludes that "the validation of any genetic signal is likely confounded by genetic and phenotypic heterogeneities which are influenced by epistatic, epigenetic and gene-environment interactions" (Lee , Woon et al, 2011). Another review (Barnett & Smoller, 2009) states "it is now widely accepted that the genetic liability to bipolar disorder reflects the action of many genes of individually small effect", similar to ADHD.

Similarly there appears to be a strong hereditary component to the etiology of conduct disorders and the related category of oppositional defiant disorders, although with gathering evidence of significant interaction and modification by environmental factors, perhaps modified by epigenetic mechanisms. According to Volkmar & Martin, there is an estimated hereditable component of "about 50%" and "genetic factors can interact with environmental factors and.... appear weaker in children coming from supportive environments". A classic 2002 paper in Science (Caspi, McClay et al, 2002) found association with a functioning polymorphism in the gene encoding monamine oxidase A, a neurotransmitter-metabolizing enzyme. Maltreated children with high MAOA expression were less likely to develop antisocial behavior. Another study found a modest association of violent behavior and serotonin dysfunction mediated by genetic polymorphisms associated with serotonin transport (Retz, et al, 2004).

There is increasing evidence for modification of genetic and biologic physiology and neurobiology by environmental mechanisms, perhaps through epigenetic mechanisms. An excellent review of "The Lifelong Effects of Childhood Adversity and Toxic Stress" from the American Academy of Pediatrics summarizes the ecology of childhood developmental outcomes and life course trajectories in an "ecobiodevelopmental framework" (Shonkoff, Garner et al, 2012). Much of this is modeled on the Lifecourse Health Development Model championed by Neal Halfon and collaborators (Halfon, Larson et al, 2013). For example, a recent study published only this year in the Proceedings of the National Academy of Sciences (PNAS) demonstrated correlation between stressful home environments and decreased length of chromosome endings(telomeres) that is moderated by genetic variation in brain serotonin and dopamine(Mitchell, Hobcraft et al, 2014).

In summary, while there is increasing evidence linking genetic influences on various mental health disorders affecting children, with the exception of some well-defined genetic disorders, these associations are varied and intermixed with environmental associations, some of which have yet to be defined and fully characterized and likely involve a complex interplay of nature and nurture.

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