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Genetics of Childhood-Onset Schizophrenia: 2019 Update

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Introduction

Childhood onset schizophrenia (COS) is defined as schizophrenia with onset prior to age 13 and is a rare and early onset variant of the much more common schizophrenia with adult onset (AOS). The prevalence of true COS cases is fewer than 1 in 10,000[1]. In contrast, the lifetime prevalence of AOS is 4.0 in 1,000[2]. It should be noted that prior to DSM-III, there was no uniform diagnostic criteria for COS. Early studies of COS therefore included children who today would receive DSM-V[3] diagnoses of Autism Spectrum Disorder, Unspecified Neurodevelopmental Disorder, or Schizophrenia, and there were significant variations between clinicians in how COS was diagnosed.

Epidemiological and family studies in the 20th century clearly established that genetic factors play a major role in the etiology of AOS. In the past decade, modern genome-wide association studies have begun to identify many specific genetic factors that are associated with AOS. Due to the low prevalence of COS, less is known about the individual genetic factors that increase risk for COS. Nevertheless, genetic studies of COS have generally paralleled studies of the much more common AOS, and initial findings suggest that many genetic factors that confer risk for AOS also confer risk for COS.

To highlight the historical evolution of genetic studies of COS, in the following, the authors will first discuss familial aggregation studies of AOS and COS. They then provide a brief overview of modern understandings of the human genome and classes of genetic variation as

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they relate to the genetic architecture of schizophrenia. The authors subsequently provide an overview of major genetic findings for AOS, including reviewing studies of common, rare, and copy number variants in AOS. Finally, the authors will review genetic studies of COS, more specifically. Of note, many modern, large-scale genome-wide association studies of schizophrenia involve minimal patient characterization aside from establishing schizophrenia case status. As such, age of onset is often not reported. Since the vast majority of schizophrenia patients have their first psychotic episode in adulthood, the authors will refer to studies of broadly ascertained schizophrenia patients as AOS studies. In addition, in the discussion of familial aggregation studies, the authors focus on studies that examined risk in parents of schizophrenia probands rather than risk in siblings, because the siblings of COS probands typically have not entered the classical age of risk for schizophrenia.

Familial aggregation of schizophrenia

Initial genetic studies of AOS and COS examined family members of patients with AOS or COS to test the hypotheses that schizophrenia and/or schizophrenia spectrum disorders show familial aggregation. Every modern study that used relatively narrow, operationalized criteria for schizophrenia found that schizophrenia strongly aggregated in families of AOS patients relative to families of community controls. Modern family studies found a three-fold increase in the relative risk (RR) for schizophrenia among parents of AOS probands compared to the parents of controls[4]. Similarly, the morbid schizophrenia risk for parents and siblings of AOS probands was 6% and 9%, respectively, compared to 1% in the general population[5]. Adoption and twin studies further suggested that the increased risk of schizophrenia among family members of AOS probands was largely due to shared genetic factors, rather than shared environmental factors[4].

In studies of COS, an early twin study found a concordance for COS diagnosis for monozygotic twins of 88.2% compared with a concordance of 22.3% in dizygotic twins[6]. This yielded a heritability estimate of 84.5%, suggesting that COS is highly heritable. Two modern studies that used DSM III-R criteria and collected data through both personal interview and interviews of family members similarly suggested that schizophrenia aggregates in the families of COS probands. Thus, the UCLA study found a RR of 17 for schizophrenia in the parents of COS probands compared to those of controls[7]. The NIMH Child Psychiatry Branch study of 95 COS patients found one case of schizophrenia in parents of COS probands and none in parents of community control probands[8]. Together, these family aggregation studies suggested that genes may play a role in the etiology of schizophrenia.

Familial aggregation of schizophrenia spectrum disorders

Family studies also found that in addition to schizophrenia, a number of other psychiatric disorders tend to aggregate in families of AOS probands. These are termed “schizophrenia spectrum disorders,” and include Schizoaffective Disorder (depressed type), Schizotypal Personality Disorder, Schizopheniform and Atypical Psychosis, and Paranoid Personality Disorder. The only two studies which determined the RR of schizophrenia spectrum disorders separately for parents (i.e., not combined with siblings) of AOS probands found

RRs of schizotypal personality and/or paranoid personality disorders of 6.6[9] and 3.0[10] in parents of AOS probands.

In the two modern family studies of COS, the RR for schizotypal personality and/or paranoid personality disorders in parents of COS probands was 10.5[7] and 15.2[8]. When schizophrenia was included as a schizophrenia spectrum disorder, the RR for schizophrenia spectrum disorders was 16.9[7] and 15.9[8] in parents of COS probands. The RR for just schizophrenia, schizotypal or paranoid personality disorders was 15.1 in parents of COS probands[7]. Compared to the RR of 5.8 for schizophrenia, schizotypal, or paranoid personality disorder found in a large family study of AOS probands that used similar diagnostic approaches as the UCLA study[9], the RR risk of schizophrenia and schizophrenia spectrum disorders appears to be greater in parents of COS probands than in parents of AOS probands. This increased rate of schizophrenia spectrum disorders in relatives of COS probands suggests that schizophrenia spectrum disorders may aggregate more strongly in the families of COS probands compared to AOS probands.

Familial aggregation of neurobiological abnormalities

A number of neurobiological abnormalities present in AOS and COS patients are also present in a substantial number of their non-psychotic first degree relatives. These abnormalities are sometimes referred to as endophenotypes. Endophenotypes are thought to reflect the effects of genetic risk for schizophrenia and are considered “intermediate phenotypes” that may be closer to the biological effects of risk genes than DSM-V symptoms of schizophrenia[11]. Some have argued that identifying endophenotypes may help elucidate causal pathways between putative risk genes and “their expression as a clinically identifiable phenotype”[12].

Abnormalities found in the non-psychotic relatives of AOS patients include impairments in neurocognitive functioning and smooth pursuit eye-movements, and abnormalities in brain structure and electrical activity[13,14]. Many similar abnormalities are found in the non-psychotic relatives of COS probands. For example, a combination of scores on three tests that detect neurocognitive deficits in non-psychotic relatives of AOS probands identified 20% of mothers and fathers of COS probands compared to 0% of the mothers or fathers of community control probands. Scores on these neurocognitive tests also showed some diagnostic specificity, with a cutoff that identified 12% of mothers of COS probands identifying 0% of ADHD mothers[15]. Non-psychotic first degree relatives of patients with COS also showed impairments in attention/executive function[16] and smooth pursuit eye tracking[17]. Non-psychotic siblings of COS probands showed deficits on a procedural skill learning task supported by a cortical-striatal network[18], widespread reductions in white matter microstructural integrity[19], and reduced gray matter volume in a number of cortical and subcortical regions, but increased grey matter volume in the lingual gyrus and cerebellum[20]. A longitudinal study also found that prior to adolescence, the non-psychotic siblings of COS probands showed reduced cortical gray matter in superior temporal and prefrontal areas[21]; however, these reductions normalized during adolescence. In general, the first degree relatives of patients with COS show subtle impairments on some tasks identified as potential endophenotypes in studies of relatives of AOS patients, suggesting that these

deficits do not merely reflect the effects of psychosis, and instead are likely to reflect genetic factors.

Interestingly, a family study of first and second degree relatives of community controls with and without family histories of schizophrenia found that impairment in neurocognitive functioning and incidence of schizophrenia spectrum disorders were relatively independent expressions of familial liability to schizophrenia[22]. Given that schizophrenia is a complex, polygenic disorder, the genes associated with neurobiological endophenotypes may not be the same set of genes that are associated with psychotic symptoms. In addition, a recent family study of COS, AOS and community control probands examined familial transmission of neurocognitive function. In AOS families, this study found shared familial effects on *attention* and *working memory*, but not on *verbal learning* and *memory for faces*. By contrast, in COS families there were significant shared familial effects on *verbal learning* and *memory for faces*, but not on *attention* and *working memory*[23]. Thus, the familial architecture of neurocognitive functions may differ somewhat between COS and AOS nuclear families.

It is important to recognize that paralleling the heterogeneity of findings in studies of COS and AOS patients, many first-degree relatives of patients with schizophrenia do not have neurobiological abnormalities. However, while there is considerable heterogeneity among relatives in what abnormalities they do have, type of neurocognitive impairment does tend to run in families. The neurobiological abnormalities identified in non-psychotic relatives of COS patients appear to tap diverse neural networks. Heterogeneity of neurobiological abnormalities may indicate that impairments in specific neural networks are associated with different sets of susceptibility genes. If this is the case, endophenotypes may help identify biologically meaningful subtypes of schizophrenia linked to specific genotypes, thereby providing a clearer link between genetic and phenotypic variation[24].

Brief Introduction to the Human Genome and Classes of Specific Genetic Variants

Recent genetic studies of AOS and COS have focused on identifying specific genetic factors that increase risk for schizophrenia. The ability to rigorously pursue such questions has accelerated rapidly since 2003, when the human genome was first sequenced and established as a reference genome to enable subsequent scientific discovery[25]. Our understanding of the range of classes of genetic variants observed in the human population; the frequency at which different classes of variants exist in the average person’s genome; and the overall genetic architecture of complex traits such as schizophrenia has improved dramatically since this landmark achievement. We now know that there are ~3 billion nucleotide base pairs (bp) in the human genome, comprised of the four nucleotide bases, adenine (A), cytosine, (C), guanine (G), and thymine (G). Approximately 1.5% of this DNA sequence encodes proteins[26], which form the building blocks of every cell and organ in the human body. A substantial portion of the remaining DNA sequence encodes non-protein coding RNA transcripts or regulatory sequences that are critical for temporally and spatially regulating the expression of the ~20,000 protein-coding genes in the human genome. However,

estimates of the exact proportion of non-protein coding DNA having a functional role vary widely (e.g., less than 10% to up to 80%[27–29]), and a significant portion of non-coding DNA likely has no functional role at all[29].

The vast majority of DNA sequence is identical between two individual humans (>99.8%)[30]. Nevertheless, given the total length of the human genome, the average individual differs from the reference human genome at ~4–5 million locations in the genome[30], yielding a huge pool of variants to examine for potential association with psychiatric traits such as schizophrenia. Broadly, each variation in sequence can be categorized based on the frequency that it is observed in the population, the size and type of variant (e.g., number of affected nucleotides), and the functional consequence of the variant. Thus, common variants (i.e., traditionally defined as variants found in >5% of the population) are observed more frequently than rare variants (i.e., <0.5–1% of the population). Relatedly, single nucleotide variants (SNVs), which are called single nucleotide polymorphisms (SNPs) when they are common in a population, affect only one bp and are generally smaller or affect shorter DNA sequence than short insertions or deletions (i.e., indels; 1–49 bp in length). Short indels, in turn, are smaller than structural variants, which include inversions, translocations, deletions, and duplications of larger sequences of DNA (i.e., > 50 bp) that affect chromosomal structure[31]. Owing to the effect of natural selection, in which deleterious mutations impact the ability of an individual to mate and/or have viable offspring or are lethal altogether, common variants are less likely to have damaging effects compared to rare or de novo variants. However, new mutations, known as de novo mutations (DNMs), occur in every offspring (i.e., are not observed in either parent) and are thereby continuously introduced into the population. Thus, all individuals carry rare variants and DNMs. Indeed, while the majority of variants observed in a single individual's genome are common and small (>99.9% of variants), the average human genome also contains over 2,000 structural variants, and 40,000–200,000 rare variants (i.e., 1–4% of variants per genome)[30,7]. Regardless of variant class or the frequency that a variant is observed in a population, the ultimate importance of a given variant rests on whether it exerts a molecular or phenotypic consequence, such as by qualitatively altering the structure of a protein and/or altering its level of expression[31]. The vast majority of variants are currently thought to have benign or minimal phenotypic consequences; however, annotating the functional consequences of a variant remains a complex task, particularly for non-protein coding regions of the genome.

These advances in our understanding of the range and scale of genetic variation present in the human genome have ushered in a new era of psychiatric genetics, focused largely on using agnostic, genome-wide approaches to identify variants associated with disease, as well as understanding how disease-associated variants disrupt biological processes to eventuate in disease. Given the frequency with which variants of all classes are observed in the average individual genome, finding robust associations between individual variants and complex traits is a major challenge. However, as new tools and standards for genetic studies have been developed and refined, psychiatric genetics has begun to yield major insights into the genetic architecture and specific variants associated with complex psychiatric traits such as AOS and COS.

The New Era of Psychiatric Genomics

Psychiatric genetics in the 1990s and 2000s was dominated by small to moderately-sized studies of candidate gene and linkage studies that frequently failed to replicate[32–34]. In contrast, over the last decade, large-scale collaborative studies, often genotyping thousands to tens of thousands of minimally phenotyped patients and controls, have begun to identify many specific variants that are robustly associated with disease. The advent and eventual success of these large-scale studies was facilitated by technological improvements that dramatically reduced the cost of genome-wide genotyping and sequencing, as well as the realization that critical confounds such as SNPs occurring at varying rates in populations with different ancestries (i.e., which can lead to spurious associations if patient and control groups are not carefully matched in genetic ancestry), needed to be carefully accounted for in genetic studies[35].

Thus far, the majority of genome-wide association studies (GWAS) of schizophrenia have investigated different classes of genetic variants through independent studies (i.e., studying common, rare, or de novo variants separately). In addition, given that COS is a rare condition, existing studies largely involved AOS patients. In the following, we will therefore first review results from well-powered, seminal studies of the more typical AOS, for each broad class of genetic variants. We will also discuss evidence for the multifactorial/polygenic threshold model of risk for schizophrenia across variant classes. Finally, we will review studies that are specific to COS, as well as studies that explore genetic associations in relation to age of psychosis onset. We note that across this review of studies, we focus on findings based on genome-wide approaches, given the now well-established problems with replicability in candidate gene studies.

Overview of Genetic Studies of AOS

It is now clear that the genetic architecture of AOS is complex and high polygenic, involving hundreds to thousands of genes, with risk variants spanning the range of possible allelic frequencies and variant classes. Thus, in a seminal genome-wide association study (GWAS) of common variants in 36,989 schizophrenia cases and 113,075 controls, 108 independent loci were found to be significantly associated with schizophrenia status[36]. While each significantly associated loci was found to confer only a small increase in risk (i.e., median odds ratio (OR) per associated SNP = 1.08), when the effects of all nominally associated ($p < .05$) loci were considered together as a single polygenic risk score (PRS), schizophrenia PRS was able to explain 18.4% of the variance in case versus control status[36]. Interestingly, while 40% of the 108 significantly associated loci were located within the sequence boundaries of a single protein coding gene, the remaining associated SNPs were located in non-protein coding regions of the genome, and only 10 loci were credibly associated with non-synonymous polymorphisms predicted to directly alter the amino-acid sequence of a protein. This suggests that many common variants associated with AOS are likely to contribute to disease risk by altering the level of expression of specific proteins, rather than more directly altering protein structure. Notable genes implicated by associated loci included DRD2, which encodes the dopamine D2 receptor that is the primary target of almost all anti-psychotic drugs; numerous genes involved in glutamatergic signaling and

plasticity, including GRIA1, GRIN2A, and SRR; and genes encoding voltage-gated calcium channels, such as CACNA1C and CACNB2, thus providing genetic evidence for existing etiologic hypotheses of schizophrenia involving dopaminergic and glutamatergic signaling. These schizophrenia-associated variants were also found to map to genes that are expressed specifically in pyramidal neurons (i.e., the primary glutamatergic/excitatory neurons of the cortex), medium spiny neurons of the striatum (i.e., primary dopaminergic neurons), and cortical interneurons (i.e., primary GABAergic/inhibitory neurons)[37]. A more recent meta-analytic GWAS of common variants in schizophrenia included an additional 5,220 schizophrenia cases and 18,823 controls, and identified 145 independent loci significantly associated with schizophrenia[38]. The identified schizophrenia-associated SNPs were enriched for genes that are intolerant to mutation (i.e., found to be very rarely mutated in humans, suggesting that mutation in these genes is under strong selective pressure), genes involved in synaptic transmission, and genes that are targets of the fragile X mental retardation protein (FMRP), which is known to regulate the protein-level expression of genes involved in brain development and synaptic plasticity. Together, these seminal studies provided compelling evidence that common risk variants for schizophrenia converge onto neuronal and synaptic gene-sets. As sample sizes continue to increase, the number of common variants significantly associated with AOS will continue to increase, along with our understanding of the convergent biological processes impacted by risk variants for AOS.

Studies of rare variants have also yielded insights into the genetic etiology of AOS, although given the inherent low frequency of individual rare variants, disease associations are generally tested after aggregating variants to summary levels such as the gene or gene-set level. Thus, schizophrenia patients have been found to carry an increased burden of rare[39] and ultra-rare[40] deleterious mutations, overall, compared to controls, although the effect size of this overall increased burden is relatively small (e.g., OR = 1.07 for damaging and disruptive ultra-rare variants[40]). Nevertheless, aggregated at the gene-set level, rare deleterious mutations in schizophrenia patients were found to be enriched for genes that are intolerant to mutation, genes that are expressed specifically in neurons, gene targets of FMRP[41], and genes that are components of synaptic gene-sets, such as the N-methyl-D-asparate receptor (NMDAR) and activity-regulated cytoskeleton-associated protein (Arc) complexes[39,40,42], which are critically involved in modulating synaptic plasticity. Protein-altering DNMs in schizophrenia patients have been found to be similarly elevated in genes involved in neuronal and synaptic function, including genes that are components of the post-synaptic density, the NMDAR and Arc complexes, and targets of FMRP[43], as well as among genes involved in regulating the expression of other genes[44]. Thus, compelling evidence indicates that damaging rare variants and DNMs in AOS also converge on genes involved in neuronal and synaptic function.

Copy number variants (CNVs) are a particular class of structural variants in which large segments of DNA are deleted or duplicated, resulting in genomic imbalances in the normal number of copies of DNA in the region. CNVs frequently arise in genomic “hotspot” regions that contain repeats of DNA sequence, known as segmental duplications, as these repeat DNA sequences make them prone to unequal crossing over during meiotic recombination (i.e., non-allelic homologous recombination). As an overall class, large (e.g., > 100 kb), rare CNVs (i.e., observed in <1% of the population) have been consistently associated with

schizophrenia (e.g., OR = 1.15;[45,46]) and have yielded important insights into the genetic etiology schizophrenia[45–50]. The overall increased burden of CNVs associated with schizophrenia is concentrated in CNVs that overlap genes[48] and several recurrent CNV loci have been associated with schizophrenia, including deletions at the 22q11.2, 2p16.3 (NRXN1), 3q29, 15q11.2, and 15q13.3 loci, duplications at the 16p11.2 and 7q11.23 loci, and deletions or duplications at the 1q21.1 and 7p36.3 (VIPR2) loci. About 2.5% of schizophrenia patients are estimated to carry CNVs at one or more schizophrenia-associated loci[49]. Interestingly, CNVs at many of these specific loci have pleiotropic effects, as they are also associated with broader neurodevelopmental disorders such as autism spectrum disorder (ASD) and intellectual disability (ID)[47,51,52]. Similar to common variants associated with schizophrenia, as well as other rare and de novo variants, schizophrenia-associated CNVs disproportionately affect neuronal and synaptic gene-sets[53], including components of the postsynaptic density, and NMDAR and Arc complexes,[47,54], and sets of genes that are involved in excitatory and inhibitory neurotransmission[55].

Notably, while at the clinical population level, common variants are expected to account for the largest proportion of overall genetic liability for schizophrenia (30–50%), each individual common variant confers only a small increase in risk[36]. Conversely, deleterious rare, de novo, and copy number variants may account for a smaller proportion of schizophrenia liability at the clinical population level; however, when present in a given individual, deleterious rare variants can increase risk substantially (e.g., ORs up to ~20–68 for the most highly penetrant CNVs[48]). Growing evidence also indicates that common and rare variants interact to increase risk. Thus, the total burden of common schizophrenia-associated risk alleles that a given individual carries can be summarized by their schizophrenia PRS, which is calculated as their weighted sum of schizophrenia risk-associated SNP alleles based on recent GWAS (e.g.,[36]). While schizophrenia patients have higher PRS than controls, regardless of CNV carrier status, patients who carry risk CNVs that have been previously associated with schizophrenia have lower PRS compared to patients without risk CNVs[56,57]. Furthermore, the elevated burden of common schizophrenia risk alleles in patients who also carry risk CNVs was found to be inversely proportional to the effect size of the risk CNV[57]. Similarly, schizophrenia patients with damaging de novo variants in genes that are intolerant to mutation or are associated with neurodevelopmental disorders more broadly, were found to have lower transmission of schizophrenia PRS from parents compared to patients without de novo variants in these genes[58].

Together, these findings suggest that there is significant heterogeneity in the specific risk variants carried by each individual AOS patient, and that risk variants converge across variants classes and the allelic frequency spectrum to increase risk in an additive manner. Overall, this is consistent with long-standing multifactorial/polygenic threshold models of schizophrenia which postulate that schizophrenia results when an accumulation of risk factors crosses a threshold of liability[59].

Genetic Studies of COS

Given that COS is rare, there are relatively few genetic studies of COS, and the majority of these focused on establishing the extent to which risk for COS is conferred through similar

genetic mechanisms as AOS. Interestingly, preliminary evidence suggests that in addition to sharing genetic risk factors with AOS, the genetic architecture of COS may include greater loading from variants that also confer risk for other neurodevelopmental disorders, such as ASD, ID, and epilepsy. Thus, in a study of 130 COS probands and 103 of their healthy siblings, COS probands were found to have significantly higher schizophrenia PRS than their siblings, as well as higher polygenic risk for ASD[60]. Elevated rates of large CNVs have also been found in COS[50], including in CNVs associated with schizophrenia and other neurodevelopmental disorders. Of note, rates of large, rare CNVs appear to be higher in COS patients compared not only to controls, but also to patients with AOS. Thus, 11.9% of COS probands were estimated to have a neurodevelopmental disease-associated CNV compared to 1.5% of their healthy siblings and 1.4%−4.9% of adult-onset schizophrenia patients[61–63]. In particular, a high number of COS probands have been found to carry CNVs at the well-known 22q11.2 locus, which is known to increase risk for multiple psychiatric and developmental disorders, including schizophrenia, ASD, ID and attention deficit hyperactivity disorder[61–63].

Studies of DNMs using exome sequencing in COS have been small; however, one study of 17 COS proband-parent trios found an overall protein-coding DNM rate of 1.17 per COS exome that was similar to rates found in other psychiatric diseases[64]. Interestingly, DNMs in COS patients were found to be enriched in loss-of-function intolerant genes, similar to AOS and other neurodevelopmental disorders[64]. Numerous DNMs were found in these small COS samples that affect genes implicated in broader neurodevelopmental disorders, including ATP1A3, which encodes a subunit of the neuron-specific ATP-dependent transmembrane sodium-potassium pump[65,66]; UPF3B, which is involved in regulating nonsense-mediated decay of mRNAs[67]; SRCAP, which is a component of the chromatin-remodeling SRCAP complex and can function as a transcriptional activator in Notch- and CREB-mediated transcription; and PNKP, which is involved in DNA-strand repair (Sanders: personal communication). Together, these initial studies suggest that DNMs in COS are enriched for neurodevelopmental-disorder associated genes; however, further research is needed to systematically test this specific hypothesis.

Interestingly, two moderately sized, independent studies (i.e., 2762 cases and 3187 controls[68] and 1067 patients and 1169 controls[69]) that largely involved AOS patients found that earlier age of psychosis onset was *not* associated with higher schizophrenia PRS. Conversely, in one of these studies that also assessed environmental risk factors, a high loading of environmental risk from perinatal insult, head injury, and/or cannabis use *was* associated with earlier psychosis onset[69]. Given that “earlier-onset” patients in these studies appeared to generally involve patients with adolescent or early-adult onset, this raises the intriguing possibility that the risk architecture of psychosis onset falling within an intermediate, adolescent range may include a greater accumulation of risk from environmental factors compared to later psychosis onset in early- to mid-adulthood. Conversely, as noted above, the genetic architecture of COS may be characterized by a joint loading of variants that confer risk for AOS, as well as variants that are strongly associated with early-onset neurodevelopmental disorders such as ASD and ID. This is consistent with the elevated rates of autism spectrum or pervasive developmental disorder diagnoses found among COS patients[70–72]. Together, this raises the possibility that different genetic and

environmental risk architectures may underlie childhood-, versus adolescent-, versus adult-onset of schizophrenia. However, this is largely speculative. Large-scale studies that concurrently assess various environmental risk factors and a comprehensive range of genetic variants associated with AOS and early neurodevelopmental disorders in large samples of schizophrenia patients whose ages of onset span the full range possible are needed to elucidate the risk architecture and specific genetic variants underlying variation in age of psychosis onset.

Summary and Implications for Clinical Practice

Overall, the extant literature suggests that the risk architecture of COS involves contributions from common variants that are associated with AOS, common variants that are associated with ASD, and a potentially higher contribution from large, rare CNVs that are associated with multiple neurodevelopmental disorders including schizophrenia, ASD, and ID, relative to AOS.

As the cost of genotyping and sequencing continues to fall, and our knowledge of the genetic etiology of COS, specifically, as well as schizophrenia, more broadly, and other neurodevelopmental disorders continues to improve, the promise of using genetic information to refine our diagnostic categories and develop individualized treatments for COS is increasingly salient[73]. Indeed, harnessing the power of next generation sequencing to accelerate biomedical discovery and develop better targeted treatments that leverage genetic and molecular information at the individual patient level is a driving force behind the 2015 NIH Precision Medicine Initiative[74]. Precision medicine approaches have already been incorporated into drug discovery trials and patient care in other areas of medicine. This is most notable for cancer, where screening for known highly penetrant genetic mutations and molecular profiling of tumors is beginning to impact clinical decision-making and guide the development and use of targeted therapies for specific tumor subtypes[75–77].

The path to precision medicine in psychiatry has a considerable way to go before gene discovery successes are translated into individualized treatments. Nevertheless, one early target for genomic screening might be for COS patients with notable developmental characteristics, such as facial dysmorphology, intellectual disability, language delay, or health problems such as congenital heart defects that are linked to CNV-related syndromes (e.g., 22q11.2, 3q29, or 15q11.2 deletion syndrome). Even in the absence of current, direct treatment implications, genetic testing to assess for the presence of potential pathogenic CNVs may be useful for improving patient and caregiver knowledge of disease etiology, as well as improving accessing to medical benefits and social services[78,79]. As major advances in gene discovery continue in the coming years, identifying convergent pathways through which multiple genes associated with COS adversely impact brain development and function offers great promise for developing novel therapeutic targets for this debilitating condition.

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Key Points

1. Childhood-onset schizophrenia (COS) shares considerable genetic overlap with adult-onset schizophrenia (AOS).
2. The risk architecture of COS involves common and rare variants, including copy number variants (CNVs).
3. COS shares genetic overlap with earlier-onset neurodevelopmental disorders, such as autism spectrum disorder (ASD).
4. The utility of genetic screening for diagnosis and individualized treatment is currently limited; however, genetic testing may be useful in some cases and identifying common neural pathways upon which risk variants act offers promise towards developing novel interventions.

Synopsis

The genetic architecture of schizophrenia is complex and highly polygenic. This review discusses key findings from genetic studies of childhood-onset schizophrenia (COS) and the much more common adult-onset schizophrenia (AOS), including reviewing familial aggregation studies and studies of common, rare, and copy number variants. Extant literature suggests that COS is rare variant of AOS involving greater familial aggregation of schizophrenia spectrum disorders and a potentially higher occurrence of pathogenic copy number variants. The direct utility of genetics to clinical practice for COS is currently limited; however, identifying common pathways through which risk genes affect brain function offers promise for novel interventions.