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# Genetics of Childhood Onset Schizophrenia

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## Synopsis

Schizophrenia is a highly heritable disorder. The genetic architecture of schizophrenia is complex and heterogeneous involving both common and rare allelic variants. Given the low prevalence of childhood-onset schizophrenia (COS), relatively few studies have examined the genetic architecture of COS. This review discusses genetic studies of COS and compares findings in familial aggregation, common allele and rare allele studies of COS to those for adult onset schizophrenia (AOS). Overall, the extant literature suggests that COS is a rare variant of AOS with greater familial aggregation of schizophrenia spectrum disorders and a higher occurrence of rare allelic variants. Given the complex genetic architecture of schizophrenia, the utility of genetic screening for diagnosis and individualized treatment is currently limited; however, identifying common pathways through which multiple genes adversely impact neural systems offers great promise towards developing novel pharmacologic interventions.

### Keywords

childhood-onset schizophrenia; genetics; common alleles; GWAS; copy number variants; rare alleles; autism

## Overview

Childhood onset schizophrenia (COS) is an early onset variant of the much more common schizophrenia with adult onset (AOS). Schizophrenia with onset prior to age 12 is infrequent. The prevalence rate 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



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was no uniform diagnostic criteria for COS. Thus, "early studies of COS included children who today would receive DSM-IV[3] diagnoses of autistic disorder, pervasive developmental disorders (PDDs), schizophrenia, or disintegrative psychosis. In addition, there were significant variations among clinicians in how childhood schizophrenia was diagnosed."[4]

Epidemiological and family studies clearly indicate that genetic variations play a major role in the etiology of AOS. Due to the low prevalence of COS, much less is known about the role of genetic variations in COS. This paper summarizes what is known about the role of genetic variations as risk factors for COS and compares results of genetic studies of COS to those of AOS. Genetic studies of COS parallel genetic studies of the much more common schizophrenia with adult onset. Many genetic studies of COS were designed to determine if the same genetic risk factors present in AOS occurred in COS. The question underlying many of these studies was whether COS was a variant of AOS. To highlight the historical evolution of genetic studies of COS we will review three classes of genetic studies: familial aggregation studies, common allele studies, and rare allele studies, in the order in which they historically occurred. Of note, the siblings of probands with COS typically have not entered the classical age of risk for schizophrenia. Consequently, in the current paper review of familial aggregation of schizophrenia related diagnoses and neurobiological abnormalities in relatives of AOS and COS probands will focus on studies that examined risk in parents of probands separately from risk in siblings.

## Familial aggregation studies

The first genetic studies of AOS and COS examined family members of patients with AOS or COS to test the hypotheses that schizophrenia, schizophrenia spectrum disorders, and neurobiological abnormalities related to schizophrenia showed familial transmission.

### Familial aggregation of schizophrenia

Every modern study that has used relatively narrow, operationalized criteria for schizophrenia and collected data through both personal interview and interviews of family members has found that schizophrenia strongly aggregates in families of patients with AOS relative to families of community controls. Adoption and twin studies suggest that genetic factors greatly increase the risk of schizophrenia.[5] Modern family studies showed a three-fold increase in the relative risk (RR=risk in relatives of AOS probands versus risk in relatives of community controls) for schizophrenia in parents of schizophrenia probands.[5] The morbid risk for parents of AOS probands is 6% compared to 9% for siblings.[6] Thus, there are significant differences in the risk for schizophrenia in the parents and siblings of probands with AOS.

Two early studies[7,8] that used different diagnostic criteria for COS than were employed by modern studies found that rates of schizophrenia in families of COS probands were comparable to rates in AOS probands. One study[7] did not use operationalized criteria for schizophrenia but rather simply stated that the children had psychotic symptoms. While the other study[8] predated DSM-III it required that to be diagnosed with COS children had hallucinations, delusions or formal thought disorder but the criteria for these symptoms were not operationalized. An early twin study[7] found a concordance for COS diagnosis for monozygotic twins of 88.2% compared with a concordance of 22.3% in dizygotic twins resulting in an estimate of heritability of 84.5%. Two modern studies used DSM III-R and collected data through both personal interview and interviews of family members. The UCLA study[9] found a RR of 17 for schizophrenia in parents of COS probands. The NIMH Child Psychiatry Branch[10] study of 95 patients with COS found only one case of schizophrenia in parents of COS probands and none in parents of community control probands.

### Familial aggregation of schizophrenia spectrum disorders

Modern family studies find 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". The narrow schizophrenia spectrum includes 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[11] and 3.0[12] in parents of AOS probands.

In the two modern family studies of COS probands, the RR for schizotypal personality and/or paranoid personality disorders in parents was 10.5[9] and 15.2.[10] In addition, there was a RR of 5.6 for avoidant personality disorder.[9] When schizophrenia was included as a schizophrenia spectrum disorder, the RR for schizophrenia spectrum disorders was 16.9[9] and 15.9[10] in parents of COS probands. The RR for just schizophrenia, schizotypal or paranoid personality disorders was 15.1 in parents of COS probands.[9] Compared to the RR of 5.8 for schizophrenia, schizotypal, or paranoid personality disorder in a large family study of AOS probands that used similar diagnostic approaches as the UCLA study,[11] the RR risk of schizophrenia and schizophrenia spectrum disorders appears to be considerably greater in parents of COS probands than in parents of AOS probands. The increased rate of schizophrenia spectrum disorders of COS probands clearly is consistent with familial transmission. The much greater concordance for schizophrenia in monozygotic than dizygotic twins in the Kallman twin study[7] suggests that schizophrenia is highly heritable in COS.

### Familial aggregation of neurobiological abnormalities

A number of neurobiological abnormalities present in patients with AOS are also present in a substantial number of their non-psychotic first degree relatives. These abnormalities are sometimes referred to as endophenotypes. Endophenotypes are features that lie intermediate to the phenotype and genotype of schizophrenia[13] and are therefore hypothesized to be closer to the biological effects of schizophrenia genes than are DSM-IV[3] symptoms of schizophrenia. Given the complexity of the genetic architecture and the heterogeneity of schizophrenia, some have argued that identifying endophenotypes may help in elucidating the causal pathways between putative risk genes and "their expression as a clinically identifiable phenotype."[14]

Abnormalities found in the non-psychotic first-degree relatives of AOS patients include impairments in neurocognitive functioning, abnormalities in smooth pursuit eye-movements, brain structure, brain electrical activity, and autonomic activity. Many of the abnormalities found in non-psychotic relative of AOS probands are also 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. There was some diagnostic specificity of the neurocognitive impairments: 12% of mothers of COS probands were identified compared to 0% of ADHD mothers. Similarly, a cutoff that identified 2% of the fathers of ADHD probands classified 17% of the fathers of COS probands.[15]. Non-psychotic first degree relatives of patients with COS showed impairments on a measure of attention/executive function[16] and in smooth pursuit eye tracking,[17] and non-psychotic siblings of COS probands showed deficits on a procedural skill learning task supported by a cortical-striatal network.[18] A longitudinal study[19] found that prior to adolescence the non-psychotic siblings of patients with COS show reduced cortical gray matter in the superior temporal prefrontal areas, but that this reduction normalizes during adolescence. In general, the first degree relatives of patients with COS show subtle impairments on some of the tasks identified as potential endophenotypes in studies of relatives of AOS patients.

The presence of these neurobiological abnormalities in non-psychotic relatives of COS patients clearly indicates that they do not merely reflect the effects of psychosis. Moreover, a family study of first and second degree relatives of community control probands with and without family histories of schizophrenia[15] found that impairments in neurocognitive functioning and schizophrenia spectrum disorders were relatively independent expressions of familial liability to schizophrenia. 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.

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. In addition, there is considerable heterogeneity among relatives who do show neurobiological abnormalities in what abnormalities they have. Not all relatives show the same abnormalities. The neurobiological abnormalities identified in non-psychotic relatives of COS patients appear to tap diverse neural networks. It remains to be seen if there is a common pathway for the neural networks underlying these neurobiological abnormalities. Alternatively, the 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 might identify biologically meaningful subtypes of schizophrenia linked to specific genotypes thereby providing a clearer link between genetic and phenotypic variation.[20]

## Studies of common alleles

Studies of complex diseases, including AOS, have been guided until very recently by the common disease/common variant hypothesis. This hypothesis proposes that common polymorphisms, classically defined as genetic variants present in more than 1 percent of the population, might contribute to susceptibility to common diseases.[21] The common disease/ common variant hypothesis was stimulated by findings from population genetics that humans have limited genetic variation: most genetic variation in an individual is shared with other members of the species. Indeed, studies of some common genetic variants for diseases such as age-related macular degeneration, type 2 diabetes, and Crohn's disease have identified numerous common variants associated with increased risk for these complex, polygenic diseases.[21] However, in most complex, polygenic disorders, each variation has a small effect on the disease phenotype. It is believed that one of the reasons these polygenic diseases are not rapidly removed through selection is that so many genes influence the phenotype.

Due to the low incidence of COS there are relatively few molecular genetic studies of COS. Of the existing studies, the majority employed a candidate gene approach to examine whether common genetic polymorphisms are associated with COS. The candidate gene approach uses a limited number of single nucleotide polymorphisms (SNPs) to tag common variations in genes selected on an a priori basis. Candidate genes selected for investigation in these studies were chosen largely based on positive associations in AOS samples. A summary of the positive gene associations with COS is shown in Table 1.

The National Institutes of Mental Health Child Psychiatry Branch (NIMH) COS study is the largest and most thoroughly characterized sample of COS individuals to date. Initiated in 1990, the investigators genotyped COS probands and their parents to determine whether specific genetic polymorphisms were associated with proband status using family-based transmission tests. Results indicated that COS was significantly associated with common polymorphisms in G72/G30,[22] GAD1,[23] dysbindin,[24] and NRG1.[25] Of note, polymorphisms in these genes were also associated with neurobiological and clinical features in COS probands. COS individuals with the NRG1 risk alleles showed larger gray and white matter volume in childhood and a steeper rate of volume decline into adolescence relative to COS individuals without these risk alleles.[25] Similarly, GAD1 polymorphisms were associated with increased rate of frontal gray matter volume loss.[23] G72/G30 risk alleles were associated with later age of onset and better premorbid functioning in these individuals.[22] Additionally, the dysbindin allele was also associated with later age of onset.[24] Other candidate gene studies of COS and early onset schizophrenia (EOS) individuals using independent samples have compared the frequencies of gene polymorphisms in COS/EOS cases versus healthy controls. Results from these studies indicated that COS was associated with a polymorphism in the tryptophan hydroxylase gene in a Japanese sample[26] and with the ValVal polymorphism of the BDNF gene in a Russian sample.[27]

## Genome Wide Association Studies (GWAS) of AOS

In contrast to candidate gene studies, which examine a limited number of SNPs, GWAS studies use a much broader array of SNPs to systematically examine the entire genome independent of any prior hypotheses about susceptibility genes. GWAS approaches are particularly important in studies of schizophrenia because our limited knowledge about the pathobiology of this disorder severely constrains our ability to choose high quality candidate genes. However, because of the large number of statistical comparisons that are made, strict thresholds of statistical significance are required that place a premium on large sample sizes.[28] Taken collectively, the NIMH COS and UCLA studies have collected data from less than 200 COS patients. Given that an AOS study with a sample size of 16,161 participants did not yield a genome wide significant result,[28] clearly the COS samples cannot yet support a GWAS study.

Given the similarity of results of familial aggregation and candidate gene studies of COS and AOS probands, it is reasonable to expect that the results of GWAS studies of AOS patients might extend to COS patients. Recent reviews and meta-analysis of GWAS studies of AOS probands[28,29] have concluded that:

1. there is a genome wide significant association between AOS and the major histocompatability locus on chromosome 6p with an odds ratio of 1.14 to 1.16, as well as with TCF4, a neuronal transcription factor implicated in neurogenesis.
2. The data support a polygenic model of AOS, involving hundreds of genes with very small individual effects; polygenic variants collectively account for approximately 30% of the total variation in genetic liability to schizophrenia and much of the genetic variation in schizophrenia is not accounted for by variations in common alleles.
3. GWAS results have frequently not supported prior reports of associations to classical candidate genes
4. There is genetic overlap of schizophrenia with autism and bipolar disorder.

## Studies of Rare Alleles

An alternative to the common disease/common allele model is the common disease/rare variant model.[30] Rare alleles are classically defined as genetic variants with a minor allele that occurs in less than 1 percent of the population.[30] As applied to schizophrenia this model hypothesizes "that some mutations predisposing to schizophrenia are highly penetrant, individually rare, and of recent origin, even specific to single cases and families."[31] A major focus of studies of rare variants in schizophrenia has been copy number variations (CNV). The development of microarray based methods for conducting genome wide scans for structural variants allowed for higher resolution exploration of the structure of chromosomes that led to the discovery that variation in the number of copies of large stretches of DNA (i.e. fewer or more than the expected two copies) is present in the normal population and also contributes to genetic risk for complex illnesses. CNVs are stretches of genomic deletions and duplications ranging from 1kb to several Mb, and thus are likely to have larger phenotypic effects than SNPs. Studies of CNVs have begun to change our understanding of the genetic architecture underlying psychiatric illnesses. In addition to the role of common genetic variants in the genetic architecture of AOS and COS, increasing research now points to a key role for variation in chromosomal structure as well.[32]

The first major study[31] of rare structural variants (i.e. microduplications and microdeletions) in schizophrenia compared the overall frequency of CNVs in patients with AOS, COS and ancestry matched controls. Fifteen percent of schizophrenia patients with onset after 18 years of age had novel structural variants compared to 5% of controls. Patients with earlier ages of onset had increased frequencies of novel structural variants. Twenty percent of schizophrenia patients with age of onset prior to 18 years of age and 28% of COS patients carried one or more rare structural variants. Almost every rare structural variant identified in patients was unique. Some "deletions and duplications were multiple megabases in size; other variants altered only one or a few genes" The mutations found in schizophrenia patients disproportionately affected genes involved in signaling networks that control brain development, especially those involving neuregulin and glutamate pathways.[31]

The NIMH COS study found that of 96 COS patients, 10% showed large chromosomal abnormalities, including 4 individuals with the 3Mb 22q11.21 deletion, 3 individuals with sex chromosome abnormalities, and 2 individuals with 500-kb duplications at 16p11.2; all at rates significantly higher than those seen in the general population or in AOS.[33] Two novel duplications disrupting the MYT1L gene on chromosome 2p25.3, one 2.5-mB deletion on chromosome 2q31.2-31.3, one novel 115-kb deletion on NRXN1, and one 120-kb duplication overlapping exons in the SRGAP3 gene on chromosome 3p25.3 were also found in additional COS patients.[33]) Individual case reports have identified additional rare and de novo mutations in other COS individuals including a novel frameshift mutation in UPF3B,[34] a de novo missense mutation in the gene encoding SHANK3[35] and a 1.58 Mb de novo 3q29 deletion encompassing numerous genes.[36]

As noted above the concordance rates for schizophrenia are much greater than expected in monozygotic than dyzygotic twins.[7] Deleterious de novo mutations which enter the gene pool for only a brief time because they reduce fecundity are therefore rarely transmitted may be the simplest way to account for large discrepancies between MZ and DZ concordance rates.[37] A similar MZ/DZ pattern is observed in twin studies of autism and AOS, disorders for which de novo variation has already been demonstrated to be a significant contributor.[38] In line with this, the majority of COS cases in the NIMH and UCLA cohorts are apparently sporadic even after detailed diagnostic evaluations of family members were conducted.

Furthermore, there is a strong monotonic increase in the risk for AOS with increasing paternal age. One explanation of this finding is that older fathers have a higher rate of de novo mutations. That sporadic cases of AOS had significantly older fathers than cases with a family history of schizophrenia "supports the hypothesis that de novo mutations contribute to the risk of sporadic schizophrenia."[39] The effect of paternal age on risk for COS has not been rigorously examined.

## Gene-Environment Interaction

A widely accepted working model of schizophrenia hypothesizes that abnormalities during embryonic brain development are caused by genetic variations. "Environmental insults such as fetal hypoxia during delivery and infection in the second trimester of pregnancy interact with the genotype to produce the neuropathology and cognitive deficits."[6] In AOS a history of obstetric complications is associated with having an earlier age of onset of schizophrenia than in patients without a history of obstetric complications.[40]

The NIMH COS study did not find an increased rate of obstetric complications in COS probands.[41] In contrast, a Japanese study[42] found increased rates of obstetric complications, particularly for boys, in patients with COS compared to children with other psychiatric disorders. Histories of obstetric complications are found in children with a number of neuropsychiatric conditions besides COS. Neither study examined whether obstetrical complications interacted with family history of schizophrenia.

## Pleiotropy: Overlap with Autism

Variation in a gene can result in multiple phenotypes. This is referred to as pleiotropy. For example, in humans, colon/lung cancer and familial Parkinson's disease are both associated with variations in the PARK2 gene.[43] Based on phenomenological and follow-up data in DSM-IV autism and schizophrenia are separate and distinct disorders. Molecular genetic studies, however, suggest considerable overlap between these disorders. Forty five genes have been evaluated for positive associations with both autism and AOS or COS. Although failures to replicate have been common, at least 20 of these genes were positively associated with both autism and schizophrenia, two genes were positive for autism and not schizophrenia, 11 genes were positive for schizophrenia and not autism, and 12 genes were negatively associated with both disorders.[44] Moreover, there are elevated rates of rare CNVs that sometimes overlap in children with autism and children with schizophrenia.[36,45] Thus, increasing evidence suggests some overlap in genetic risk for COS and autism.

## Summary

Schizophrenia (AOS and COS) is a highly heritable disorder with a heterogeneous genomic architecture. Like autism there are at least two distinct genetic mechanisms for acquiring schizophrenia, one through de novo mutations resulting in rare alleles in simplex families, and one through inheritance of common alleles of small effect in multiplex families. The majority of the mutations associated with schizophrenia are currently thought to be rare alleles.[46]

The adult- and childhood-onset forms of schizophrenia appear to overlap genetically. To date, the differences between AOS and COS appear to be quantitative. There is a greater aggregation of schizophrenia and schizophrenia spectrum disorders in first degree relatives of patients with COS compared to first degree relatives of patients with AOS. In addition, the occurrence of rare alleles, mostly de novo, appears to be higher in patients with COS compared to patients with AOS. Other than these quantitative differences, however, genetic studies have offered little insight thus far into why in rare cases, the first onset of schizophrenia occurs prior to adolescence. This is perhaps the most interesting questions to be addressed in future genetic studies of COS.

The recent findings on common and rare alleles shed light on a question that has long puzzled geneticists. How has schizophrenia persisted in the gene pool given the adverse effect of this disorder on fertility? Negative selection predicts the removal of most risk alleles with major deleterious effects. In schizophrenia (and other neuropsychiatric disorders such as autism) common risk alleles have small effects and alleles with large penetrance (e.g. CNVs) are rare. Multiple common alleles are required to develop schizophrenia. The increase in risk conferred by any one common allele is quite small. “Rare risk alleles are either of recent origin if highly penetrant, or older mutations with smaller effect which have not yet been eliminated by selection.”[29]

Both the common disease/common variant and rare allele models face challenges in explicating the genetic mechanisms for the transmission of schizophrenia. The common disease/common variant model accounts for a relatively small percentage of cases, and any one allelic variation, with very rare exceptions, confers only a small amount of risk for schizophrenia. Conversely, alleles with large penetrance (e.g. CNVs) are rare, and negative selection predicts the removal of most risk alleles with major deleterious effects from the population gene pool. This suggests that “the genomes of individuals with these conditions are unusually ‘fragile’.”[30]. However, “the unique phenotypes of autism, schizophrenia and bipolar disorder seem too specific for a gross molecular lesion such as global genomic instability.”[30]

The common disease/common variant and rare allele models of schizophrenia also have the challenge of explaining how either many different common alleles of small effect, or many different rare (in many cases unique) mutations can eventuate in the same clinical phenotype- schizophrenic symptoms. The mirror image challenge for both models is to account for how many of the common allelic variants and the propensity for rare variants found in schizophrenia are also frequently present in autism and bipolar disorder.

What both sets of challenges clearly indicate is that in schizophrenia, the pathways from genotype to phenotype are complex. Mapping the pathways from allelic variation to the symptoms of schizophrenia will require a deeper understanding of both the schizophrenia phenotype and the genetic mechanisms that increase risk for this disorder than implied in earlier, simpler models of the genetic transmission of schizophrenia. This process has been further complicated by research suggesting that gene expression can be regulated by genes in non-coding regions of the genome and has led to a great deal of interest in sequencing the non-coding regions to identify epistatic interactions with putative susceptibility genes. Thus, it is increasingly evident that a systems biology approach which “integrates genomic, transcriptomic, and proteomic data, metabolomics, gene networks, epigenetics and environmental factors”[29] must be integrated with data on neural networks in order to elucidate the pathways from allelic variations to specific schizophrenia phenotypes. The findings briefly summarized above on genetic mechanisms and phenotypes in schizophrenia put in focus the necessity of this approach for both COS and AOS.

## Relevance of Genetics to Clinicians/Implications for Clinical Practice

In a number of areas of medicine, genetic information is beginning to be used to refine diagnoses and individualize treatment. For example, BRCA mutation in either of the BRCA1 or BRCA2 genes can result in a hereditary breast-ovarian cancer syndrome that accounts for five to ten percent of breast cancer cases in women. Approximately 50% to 65% of women born with a deleterious mutation in BRCA1 and 40% to 57% of women with a deleterious mutation in BRCA2 develop breast cancer by age 70. In addition, there are implications for prognosis and treatment of having a BRAC1 vs BRAC2 mutation. For example, “multiple lines of evidence indicate that women with BRCA1-related BC may derive less benefit from taxane-based treatment than other categories of BC patients.”[47] In contrast to BRAC1 and BRAC2 mutations in breast and ovarian cancer, the allelic mutations associated with increased risk for schizophrenia detected so far offer little immediate prospect for helping to refine diagnosis or guide treatment. Each individual mutation in common alleles has a very small effect on risk for schizophrenia and it appears that some combination of multiple common alleles is required to substantially increase schizophrenia risk. Conversely, rare alleles, while they may have much larger effects on risk, are idiosyncratic and therefore not useful in screening populations for schizophrenia risk. In line with this complexity and heterogeneity of genetic risk for schizophrenia, individualized treatment based on knowledge of individual genotypes appears an unrealistic goal for the foreseeable future.

In contrast, elucidating the neurobiological pathways from genes to specific schizophrenia phenotypes offers a remarkable opportunity to identify new therapeutic targets for drug development. This is of vital interest because of our current very limited understanding of the pathobiology of schizophrenia. Our limited understanding of the pathobiology of schizophrenia importantly stems from the absence of good animal or molecular models of schizophrenia. Identifying the common pathways through which multiple genes adversely impact complex neural systems offers great promise in beginning to identify new 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. Causal genes for COS appear to involve both common and rare genetic variants
3. COS is associated with greater familial aggregation of schizophrenia spectrum disorders and a higher rate of rare allelic variants than AOS
4. COS shares genetic overlap with autism
5. The current utility of genetic screening for diagnosis and individualized treatment is limited; however, identifying common neural pathways upon which multiple genetic variants act offers great promise towards developing novel pharmacologic interventions.

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## SUMMARY

**Implications for Clinical Practice**

- COS is a rare variant of AOS
- COS shares genetic overlap with autism
- Causal genes for COS include both common variants of small effect and rare variants with larger effect
- The current utility of genetic screening for COS diagnosis and individualized treatment is limited
- Identifying common neural pathways upon which multiple genetic variants act offers promise towards developing novel pharmacologic interventions

**Table 1**

Genes associated with childhood-onset and early-onset schizophrenia in candidate gene studies.

| Authors and year | Study Design | Sample | Significant Associations | Smallest p |
|---|---|---|---|---|
| Addington et al., (2004) | Family-based transmission disequilibrium for 8 G72/G30 locus and two-marker haplotypes and DAO SNPs | 53 COS probands trios, 11 COS proband dyads, 16 psychosis NOS proband trios, 8 psychosis NOS dyads (mixed ethnicity) | 3 G72/G30 locus SNPS + two 2- marker G72/G30 SNP haplotypes associated with COS; no DAO SNPS associated with COS | 0.015 |
| Addington et al., (2005) | Family-based transmission disequilibrium for 14 GAD1, all 2, 3, & 4 SNP haplotypes, and 3 GAD2 SNPs | 55 COS+ psychosis NOS trios, 11 COS+ psychosis NOS dyads (mixed ethnicity) | 3 GAD1 SNPs associated with COS, and one 4-SNP haplotype | 0.005 |
| Gornick et al., (2005) | Family-based transmission disequilibrium for 14 Dysbindin SNPs | 73 COS+ psychosis NOS proband trios, 19 COS+ psychosis NOS proband dyads (mixed ethnicity) | 1 SNP w sig. COS association: P3521; two 2-marker haplotypes containing P3521 w sig. COS association | 0.008 |
| Addington et al., (2007) | Family-based transmission disequilibrium for 56 NRG1 SNPs and 2 micosatellites | 59 COS+ psychosis NOS proband trios, 11 COS+ psychosis NOS proband dyads for TST (mixed ethnicity) | Several NRG1 SNPs and 2,3, &4 SNP haplotypes associated with COS | 0.0004 |
| Sekizawa et al., (2004) | Childhood-onset case versus Control design for Tryptophan Hydroxylase Gene Polymorphism | 51 COS (onset before 16 years) vs. 148 HCs (Japanese) | A allele relatively higher in COS than HCs (p = .097, OR: 1.47), AA genotype associated with OR = 1.97, p = .0058 | 0.0058 |
| Pakhomova et al., (2011) | Early-onset case versus control design for BDNF Val/Met polymorphism, 5-HTTLPR, type 2A serotonin receptor, T 102c, D2 dopamine receptor (Taq1A) | 65 EOS (onset before 15 years) vs. 111 HCs (Russian) | ValVal BDNF polymorphism significantly more common in EOS patients than controls | 0.03 |