

22q11 Deletion Syndrome and Forensic Research: Can We Go There?

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Chromosome 22q11 deletion syndrome (22q11DS) encompasses velocardiofacial syndrome (VCFS), DiGeorge syndrome (DGS), and conotruncal anomaly face syndrome (CTAFS). The disorder may represent the interface between genetics and brain-behavior relationships. As there is a strong relationship between the genetic syndrome and schizophrenia, individuals with the disorder are likely to be disproportionately represented in the criminal justice system. The purpose of this article is to review the 22q11DS in the context of forensic research. The existing literature regarding the syndrome and its relationship to schizophrenia is reviewed. A study design is presented to determine the prevalence of the syndrome in correctional facilities compared with expected community prevalence rates. Finally, a brief history of genetic research in correctional facilities is reviewed as a potential model to determine the feasibility of research involving 22q11DS.

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22q11 deletion syndrome (22q11DS) involves microdeletions on the long arm of chromosome 22 in area 11. These usually occur *de novo*, although 10 to 25 percent may be inherited in an autosomal dominant pattern.^{1–3} A wide variety of clinical findings have been described in affected individuals, including cardiac defects, palate anomalies, typical facial features, learning difficulties (LDs), mental retardation (MR), athymia, and characteristic physiognomy. The structures primarily affected are derivatives of the embryonic third and fourth pharyngeal arches and pouches. This suggests that haploinsufficiency (reduced gene dose) of two to three millibases^{3–5} is important in pharyngeal arch and pouch development. Gene searches have been successful in identifying more than 30 genes in the deleted segment.⁴ Conservatively, the prevalence of 22q11DS is estimated to be 1 in 3,000⁶ to 1 in 4,000^{3,7–9} live births. However, the syndrome is likely to be underdiagnosed for several reasons. First, there is incomplete penetrance and therefore a great variation in phenotype.^{1–6} Second, fluorescent *in situ* hybridization (FISH) of chromosomal preparations is needed,

as conventional methods of chromosomal analysis do not demonstrate the microdeletion. Third, until recently, the syndrome was not widely described in the peer-reviewed literature. To date, most clinical studies have focused on children who attend clinics for craniofacial or congenital heart disorders.^{9,10}

Later-onset illnesses associated with 22q11 deletions have also been described. Thrombocytopenia,^{3,11,12} hypocalcemia,^{3,13} hypothyroidism,^{10,14} and various neurological complications^{10,15} have been associated with 22q11DS. In addition to the highly variable phenotypic expression and later-onset illnesses, there is a high prevalence of serious mental illness in adult patients with 22q11DS.

22q11DS and Mental Illness

In a review of clinical case reports on adults with 22q11DS by Cohen *et al.*,¹ 37 percent of 126 individuals suffered from a mental illness. More than one psychiatric disorder was present in 12 (27%) of the individuals. Seventy-three percent ($n = 33$) had evidence of a psychotic illness such as schizophrenia, schizoaffective disorder, or a paranoid disorder. Mood disorders, such as depression or bipolar disorder without psychosis, were present in 11 percent of the individuals. Another 16 percent of individuals had another psychiatric disorder or an unspecified behavioral problem.

In children and young adults, the 22q11DS has also been associated with high rates of a neuropsychi-

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atric disorder (56% of $n = 32$), attention deficit hyperactivity disorder (44%), autistic spectrum disorders (31%), and mental retardation, with test profiles suggestive of nonverbal learning disorders.¹⁶ While the psychiatric dysfunction among those with 22q11 DS is as varied as the phenotypic presentation, several common temperamental features have been described in studies of children and adolescents with velocardiofacial syndrome (VCFS), including poor social interaction skills, high levels of anxiety, enduring fearfulness of painful situations, behavioral excitation, exaggerated response to threatening stimuli, impulsivity, and irritability.^{17–20} These features often precede the onset of psychosis in children in whom schizophrenia later develops.^{17,20} However, individuals with a less severe phenotype of 22q11 DS are often undiagnosed until the later onset of behavioral manifestations becomes prominent.^{15,20}

Recently, a specific psychiatric entity found in children with 22q11DS has been described. Multiplex developmental disorder (MDD) has been described as a combination of several psychiatric problems that have a pervasive impact on the development of the basic skills during the first years of life. The failure to achieve developmental milestones subsequently affects social, emotional, and cognitive development.²¹

The strong association between 22q11DS and schizophrenia (22q11DS-Sz) has been well described.^{2,5,10,11,15,17–19,22–24} Approximately 25 to 30 percent of adults with 22q11DS have schizophrenia. This suggests that schizophrenia in this population is at least 25 times more prevalent than in the general community and doubles the risk for the development of the illness in a first-degree relative of an individual with schizophrenia.^{17,19,25} 22q11DS has been found in one to two percent of those with schizophrenia.^{10,18} Studies have suggested that 22q11DS-Sz may be a distinct genetic subtype of schizophrenia.^{10,22,24}

Studies disagree as to whether the schizophrenic phenotype of 22q11DS is distinguishable from other forms of schizophrenia.^{25,26} One study²² suggested that those with 22q11DS-Sz had a later age of onset and fewer negative symptoms. However, a larger study found no significant differences in the severity of core positive or negative symptoms between the 22q11DS-Sz and comparison group.²⁶ Further, no differences were found in the severity of anxiety-depression scores.

The difference in core symptoms between schizophrenia and 22q11DS-Sz is currently debatable. However, there is agreement that excitement factor scores from the Positive and Negative Syndrome Scale are significantly higher among those with 22q11DS-Sz.^{22–24} Those with 22q11DS-Sz were shown to have poor impulse control, uncooperative behavior, and hostility that differed significantly from those with non-22q11DS schizophrenia.²⁶

Neuroanatomic Correlates and 22q11DS-Sz

The results of neuroimaging among individuals with 22q11DS-Sz are qualitatively and quantitatively similar to the findings in people with schizophrenia.^{17,22} In a qualitative magnetic resonance imaging (MRI) study of 11 adults with 22q11DS-Sz, a high prevalence of white matter foci, concavum vergae/cavum septum pellucidum, sulcal and ventricular enlargement, and cerebellar atrophy were found. While no specific anatomic correlates to the deep white matter bright foci have been identified, it is a recognized nonspecific abnormality among those with schizophrenia.²⁷

Although there is some neuroanatomic correlation between adults with 22q11DS-Sz and those with schizophrenia, there is little correlation between the behavioral phenotype and the degree of deletion from chromosome 22. Individuals with similar genetic deletions and shared etiology for schizophrenia may have substantial variability in measures of brain tissue and cerebral spinal fluid (CSF) volume. This is a direct result of the heterogeneity in the expression of the genetic abnormality.²² In children and adolescents with 22q11DS in whom schizophrenia does not develop, consistent neuropsychological characteristics and behavioral phenotypes have emerged that are independent of the degree of chromosome deletion. These children and adolescents routinely display higher verbal than non-verbal IQ scores, and deficits in the areas of attention, story memory, visuospatial memory, arithmetic, and performance relative to other areas of achievement and psychosocial function.²⁸ It is believed that the behavioral phenotypes observed in children and adolescents with 22q11DS are reflective of nonverbal learning disabilities, concomitant language deficits, and social-emotional delay.

Neuropsychological functioning in adults with 22q11DS is also impaired compared with that in age-

and gender-matched control subjects. In adults with a deletion in chromosome 22, there is significant impairment in visual-perceptual ability, problem solving, planning, and abstract social thinking. It has been suggested that the haploinsufficiency of a neurodevelopmental gene(s) mapping to 22q11 underlies the cognitive and behavioral effects observed in individuals with the deletion syndrome.²⁹ Regardless of the etiology, it is noted that similar neuropsychological functioning has been described in adults with non-22q11DS schizophrenia.²⁸

Schizophrenia and Correctional Settings

It is clear that the absolute number of adults in the American correctional setting continues to increase. The point prevalence at midyear 2002 was 2.1 million adults incarcerated in federal, state (prisons), or county (jails) correctional facilities. Between 1995 and the end of 2002, the incarcerated population grew an average of 3.6 percent annually, with the largest increase among those held in federal facilities (5.8%).^{30–32} Despite the overall increase of the number of adults incarcerated, there continues to be disproportionate representation by those with schizophrenia.^{33–35}

It is well accepted that the background community rate of schizophrenia is often reported as 0.5 to 1.5 percent.³⁶ It has also been well documented that correctional facilities are collection and containment centers for those with mental illness. The numerous reasons for this phenomenon have been discussed extensively and include deinstitutionalization policies from the 1950s, mandatory incarceration for drug crimes, decreases in funding for outpatient treatment programs including outreach, and society's belief that police are the most appropriate resource to deal with an individual showing aberrant behavior. It is difficult to determine with precision the prevalence of schizophrenia among incarcerated adults. Methodological and diagnostic differences make it difficult to compare results across studies. However, it has been estimated that the current and lifetime prevalences of schizophrenia among male jail detainees are three and four percent, respectively.³¹ Among 1,272 women in the Cook County jail system, the prevalence of schizophrenia was found to be almost 2.5 percent.^{33,35}

Among incarcerated individuals, it is possible that 22q11DS-Sz is more common than expected. In part, this would be due to the increased prevalence of

individuals with schizophrenia who are incarcerated. However, it is possible that the prevalence of 22q11DS-Sz is disproportionately higher, even when considering the prevalence of individuals incarcerated who have schizophrenia. The behavioral manifestations of temper outbursts, coupled with the presence of schizophrenia, make it possible that correctional institutions have a greater prevalence of 22q11DS-Sz than expected, based on community epidemiology.

22q11DS-Sz in Correctional Facilities

Correctional facilities may well represent collection and containment centers for those with 22q11DS-Sz. Visual-spatial recognition, impairment in social learning, and delayed emotional maturation may predispose individuals with 22q11DS-Sz to impulsive behavior outbursts. Further, it is reasonable to hypothesize that behavioral dyscontrol, in the context of hostility and uncooperative behavior,²⁶ could be causally associated to the events leading to incarceration.

Methodologically, it is relatively easy to design a prevalence study to identify individuals with 22q11DS-Sz who are incarcerated and to determine if the prevalence is higher than expected, on the basis of community epidemiology. If it is assumed that the prevalence of 22q11DS-Sz is approximately the same as that in the community (the null hypothesis),³⁷ the expected prevalence of 22q11DS-Sz in any given correctional institution per year can be calculated based on several assumptions: 15 percent of those incarcerated have schizophrenia, 1 in 4,000 live births results in an individual with 22q11DS, and 25 percent of those with 22q11DS have schizophrenia.

In addition, it is relatively easy to develop a screening protocol to identify individuals with suspected 22q11DS-Sz.^{19,38} According to recommendations by Bassett and Chow,¹⁹ individuals with schizophrenia with two or more of the following phenotypes are at an increased risk for 22q11DS: (1) hypernasal speech or a history of velopharyngeal incompetence; (2) characteristic facial features such as long narrow face, narrow palpebral fissures, flat cheeks, prominent nose, small ears, and small mouth; (3) learning difficulties, a history of special education, or mild/borderline mental retardation; (4) congenital heart defect; (5) another significant congenital abnormality such as polydactyl, kyphosis or scoliosis, and renal anomaly; (6) a history of hypocalcemia and/or hypo-

parathyroidism; or (7) a history of athymia or severe immune deficiency in infancy.

A prevalence study of incarcerated adults with 22q11DS-Sz would therefore first involve identification of individuals with schizophrenia. Next, a subgroup of those with schizophrenia who met the criteria from the relatively simple screening test by Bassett and Chow¹⁹ would be identified. Blood from the subgroup would then be subjected to FISH with a fluorescently labeled probe from the 22q11.2 region to identify unequivocally the chromosomes that do not fluoresce (i.e., those with submicroscopic deletions).

Genetic Research in Correctional Facilities

Despite the relatively simple study design that could be employed to determine the prevalence of 22q11DS-Sz in correctional facilities, recent history illustrates the difficulties, limitations, and potential misuses of such forensic research.

In 1968, a landmark letter was published in *The Lancet* that described chromosomal analysis on Danish men reported to be criminally insane.³⁹ Results of chromosomal analysis of 155 men who had committed arson revealed that two individuals (1.3%) had the abnormal karyotype of 47, XYY. The community prevalence of 47, XYY was well established at 1 in 1,000 live male births, or 0.02 to 0.05 percent. As a result of the Danish work, it was suggested that the risk for an abnormal karyotype increased if the individual had committed arson.

The belief of disproportionate incarceration was perpetuated when Waltzer *et al.*⁴⁰ published work that described over-representation of 47, XYY in correctional settings. In psychiatric and penal settings, the published work suggested a three- to fourfold over-representation. In special security settings that were described as mental-penal (in essence, psychiatric facilities within a correctional setting), there was a 20-fold over-representation of 47, XYY men compared with background community rates.

Both landmark studies were subject to ascertainment bias. Most of the information was obtained from populations selected precisely because they demonstrated a particular personality or physical characteristic. Further, the early prevalence studies on XYY were case studies, not cohort studies. By design, the study started with individuals who were incarcerated, and the researchers then looked for

those with abnormal chromosomes. A stronger study design would have found individuals with abnormal chromosomes and then would have looked for criminal history. Controlled studies concerning XYY did not occur. However, researchers continued to find cross-sectional support for the belief that men with XYY genotype were over-represented in the institutions for mentally retarded individuals, mentally ill individuals, people found criminally insane, and aggressive offenders.^{39,41} Despite these findings, the XYY syndrome defense has not been successful in the five major U.S. cases that have attempted to use it. In the first case, *People v. Farley* (1969, unpublished), the jury rejected the defendant's claim that the XYY syndrome precluded him from forming the necessary intent to commit murder. The XYY syndrome was found to not meet the state's requirements for insanity and thus was not presented as evidence in the next two cases. In the fourth case, *People v. Yukl* (1975),⁴² an appeals court found that the "presently available medical evidence is unable to establish a reasonably certain causal connection between the XYY defect and criminal conduct" (Ref. 43, p 250).

22q11DS-Sz Research in Correctional Facilities

The principle rationale for research on the 22q11DS-Sz in correctional facilities is identification of those who have significant health-related problems^{3,11-15} and those who would benefit from aggressive treatment of the schizophrenia. Specifically, it has been hypothesized that the genetic basis for the schizophrenia in 22q11DS has important treatment implications. Incarcerated individuals with 22q11DS-Sz may well benefit from psychopharmacologic interventions that specifically target hostility, impulse dyscontrol, and uncooperative behavior. In addition, a prevalence study would assist in confirming or refuting the suspicion that the prevalence among those incarcerated is higher than in the surrounding community. Bassett and Chow¹⁹ set forth historical and physical features that should increase the index of suspicion for 22q11DS. Some individuals, such as those who have a cleft lip and/or have undergone palate repair for velopharyngeal insufficiency or repair of a congenital heart defect may be immediately evident with medical screening. Others, such as those with unusual facies, may be harder to discern. However, the combination of specific physical attributes and behavioral indicators or pre-

natal developmental history increases the likelihood of the presence of 22q11DS. Thus, it would be necessary only to conduct chromosomal analyses on those individuals with a high likelihood of the presence of the deletion syndrome.

A prevalence study of 22q11DS-Sz in correctional facilities would not require a control group. In addition, it is unlikely that the low IQ present for many individuals with the deletion syndrome is severe enough to affect the autonomy necessary to provide informed consent for participation in research studies. However, as with the XYY studies, such a genetic study among incarcerated individuals raises three major ethical concerns. First, it is unclear how the individual would directly benefit. It is easily argued that symptomatic schizophrenia would be recognized and treated, without the knowledge of an underlying genetic abnormality. Case law suggests that the presence of the deletion syndrome is insufficient to prove mental incompetence regarding criminal behavior. Further, it is unlikely that courts would even accept such evidence as a mitigating circumstance, as the prosecution would only need to allude to all the noncriminal members of society who also possess the deletion syndrome.

Another ethical concern regarding a prevalence study of 22q11DS-Sz among those incarcerated involves the issue of how society would benefit from such research. Clearly, there is no method to screen and identify individuals at risk for the deletion syndrome or for antisocial behavior among those with the deletion syndrome. Nor is it a factor for intervention after the commission of a crime. The simple knowledge of who has the deletion syndrome among those incarcerated is insufficient to benefit society.

Finally, the ethical principle of justice in the application of the findings must be addressed when considering such research. It is entirely unclear how the finding of the deletion syndrome applied to a unique individual would provide justice to their idiosyncratic circumstances. Nor would there be justice available to victims of the alleged crimes, based on the genetic knowledge.

In summary, it is highly possible that 22q11DS-Sz has a higher prevalence among those incarcerated than in the surrounding community. However, the application of the findings of previous genetic studies among those incarcerated, coupled with the ethical dilemmas raised by such a proposal, make it unlikely that a definitive project would be undertaken.

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