AXYS Criminal Justice Task Force White Paper

47,XXY/Klinefelter syndrome is a trisomy chromosomal aneuploidy in which the affected male has three copies of a particular chromosome instead of the usual two. Other common types of trisomy that survive birth in humans are:

· Trisomy 21 (Down syndrome)

· Trisomy 18 (Edwards syndrome) [1]

· Trisomy 13 (Patau syndrome)

· Trisomy 9

· Trisomy 8 (Warkany syndrome 2)

· Trisomy 22 (Emanuel syndrome)

· XXX (Triple X syndrome)

· XYY (47,XYY)

This paper is not intended to be a comprehensive presentation of X and Y chromosome aneuploidies ("X/Y variant"). Rather, its purpose is to serve as an educational resource provided by AXYS, with footnotes and links (where available) to peer-reviewed medical and other treatises, for those involved in the criminal justice system, including individuals with an X/Y variant and their family members and loved ones, police, judges, prosecutors, defense attorneys, social workers, parole boards and probation officers. While there is absolutely no proof that a male diagnosed with 47,XXY/Klinefelter syndrome ("47,XXY" or "KS"), or any person diagnosed with any other X/Y chromosome variant, is predisposed to criminal activity or behavior, certain cognitive, neurological and behavioral implications of KS and of the other X/Y variants are important considerations for those persons who do find themselves involved in the criminal justice system.

AXYS; AXYS Clinic and Research Consortium.

- AXYS (association for X and Y chromosome variants) is a national 501(c)(3) nonprofit organization whose mission encompasses providing information, advocacy, resources and support to individuals diagnosed with

[1] Trisomy 18 (Edwards syndrome) is the condition Senator Rick Santorum's daughter, Bella, has.

KS and other X/Y variants, their families and other impacted persons and to medical professionals, including information regarding research and clinical trials.

- AXYS also serves an important function to the medical community, both as a source of information and through its AXYS Clinic and Research Consortium ("ACRC"). ACRC is a clinical consortium that assists independent multidisciplinary and single specialty clinics committed to KS and other X/Y variant genetic conditions in collaborating with one another, sharing informational resources and exploring opportunities to participate in joint research projects. AXYS organizes annual meetings of the ACRC at which members meet to discuss research and issues important to the KS and X/Y variant community. Information regarding ACRC can be found on the AXYS website (www.genetic.org). Members of the ACRC in 2019 include:

  - Children's Hospital Colorado: eXtraordinarY Kids Clinic in Aurora, Colorado (www.childrenscolorado.org; Clinic Coordinator: 1+720-777-8361). The Director of this Clinic, which sees patients from pediatrics to young adulthood (and can also make adult referrals) is Dr. Nicole Tartaglia, M. D., a renowned leader in research and treatment of KS and other X/Y variants).
  - Johns Hopkins: 47,XXY Klinefelter Syndrome Clinic in Baltimore, Maryland (www.klinefelter.jhu.edu/klinefelter.php ; Appointments: 1+855-695-4872).
  - Stanford University School of Medicine (Clinic Coordinator: reikor@stanford.edu).
  - Nemours Alfred I. DuPont Hospital for Children: eXtraordinarY Kids Clinic (www.nemours.org).
  - Cedars Sinai, Los Angeles (Clinic Coordinator: 1+310-423-9935).
  - Emory University, The eXtraordinarY Clinic at Emory (www.genetics.emory.edu; Appointments: 1+800-366-1502).
  - Rush University Medical Center, Chicago (Appointments: Dorothy Malecki, 1+312-942-4036)
  - Weill Cornell Medical College, NY, NY (Appointments: 1+212-746-5309).
  - Wake Forest Baptist Medical Center, Wake Forest, NC (Appointments: 1+336-713-1493).
  - Children's Hospital of Philadelphia (CHOPS), (Appts: Meagan Snow-Bailey, 215-590-3174).
  - MassGeneral Hospital, Boston, MA, Klinefelter Syndrome Clinic Appointments/Clinic Coordinator: Emma Snyder, 617-726-5521
  - Cleveland Clinic, Cleveland, OH, Klinefelter Syndrome Clinic Appointments/Clinic Coordinator: Stephanie LeMasters 216-444-7987

- The National Institutes of Health in Bethesda, Maryland is engaged in ongoing research regarding X/Y variants in children, adolescents and adults and is actively recruiting for the following clinical studies:

  - National Institutes of Health, The Clinical Study of Sex Chromosome Variants, sponsored by the National Human Genome Research Institute. This study is currently recruiting adult participants (males

and females between the ages of 18-55) and includes KS and all other X/Y chromosome variants. The study lasts about 5 days and includes comprehensive testing and imaging studies of the heart, abdomen and brain. Compensation is offered to the study participant and travel, lodging and certain meals are compensated for the participant and one companion. (Clinical Trials.gov identifier: NCT01661010; the principal investigators are: Dr. Maximillian Muenke, M.D., at mamuenke@mail.nih.gov or 1+301-402-8167, and Dr. David Page, or contact the Office of Patient Recruitment at prpl@mail.cc.nih.gove or 1+800-411-1222 and refer to Study 12-HG-0181).

- National Institutes of Health, Behavioral, Cognitive, and Brain Imaging Study for Boys and Young Men with XYY, sponsored by the National Human Genome Research Institute. This study is currently recruiting male participants between the ages of 5-25. Other X/Y variants to be studied in the near future. Compensation is offered to the study participant and travel, lodging and certain meals are compensated for the participant and one companion. Principal investigator is: Dr. Armin Raznahan and the primary contact is Jonathan Blumenthal at jb364e@nih.gov or 1+301-435-4516.

- **For further information, including a professional directory, clinics which are members of ACRC and latest research and clinical trials, please visit the AXYS website at www.genetic.org or call 1-888-999-9428.**

What is 47,XXY/Klinefelter Syndrome?

47,XXY is a genetic condition in which the affected male has an extra X chromosome. Typically, a person has 46 chromosomes (23 numbered pairs of chromosomes, including the X and Y chromosomes). 47,XXY occurs as a result of failure of chromosome division (called nondisjunction) during formation of the sperm or egg, or during early cell divisions after fertilization. Past research has shown it is paternal in origin in 50% of cases and maternal in origin in the other 50%. It is not hereditary and it is not curable. It is diagnosed through a simple blood test – a chromosome analysis (called a karyotype) - and is the most common sex chromosome anomaly, affecting between 1 in 500 to 1 in 650 male babies born each year in the U.S., a frequency similar to Down syndrome (which occurs in approximately 1 in 700 babies born each year in the U.S.).[2] It is often stated that XXY is as common in the population as individuals with red hair.

Even though 47,XXY affects a substantial portion of the male population, it is a condition with a low rate of diagnosis, primarily because of substantial variation of clinical presentation.[3] It is not well understood by the public, the legal community or even the medical community in general. It is estimated that 65% of males with

[2] Gravholt C, Chang S, Wallentin M, Feder J, Moore P, and Skakkebæk, *Klinefelter syndrome – integrating genetics, neuropsychology and endocrinology*, Endocrine Reviews (March 2018); published by the Endocrine Society, https://academic.oup.com/edrv/advance-article-abstract/doi/10.1210/er.2017-00212/4847830; Verri A, Cremante A, Clerici F, Destefani V, and Radicioni, *Klinefelter's syndrome and psychoneurologic function,* Molecular Human Reproduction, Vol. 16, No. 6, pp. 425-433 (February 2010). Down syndrome is a genetic condition in which the person, as with a KS male, is born with an extra copy of a chromosome, in this case with an extra copy of chromosome 21, also referred to as Trisomy 21.

[3] Gravholt, et al., *supra* at note 2.

the condition remain undiagnosed in their lifetime.[4] KS and other X/Y variant conditions have not received the broad national attention and funding that other genetic disorders, such as Down syndrome or Fragile X syndrome, have received.

Despite the prevalence of 47,XXY males in the population, less research has been conducted and less is known about the conditions than would otherwise be expected. Particularly lacking are information, research and intervention studies that provide answers for the best ways to address treatment, leaving doctors with no recognized evidenced-based course of clinical management. As noted in the Gravolt, et al. March 2018 Endocrine Reviews article referenced in footnote 2 above, "[r]isk assessment in KS is compromised by insufficient insight into the prevalence and causes of different syndrome-associated traits that may impact adversely on prognosis. This is especially the case for genetic, endocrine, cardiovascular, neurocognitive and behavioural contributions to the wide range of diseases, that together contribute to excess all-cause mortality."[5] However, research progress is being made, although general awareness and education of medical professionals is still lacking. In March of 2016, the 2nd International Workshop on Klinefelter Syndrome was held in Munster,Germany, drawing experts from around the world to discuss current research and to address deficiencies in diagnosing and treating 47,XXY

https://genetic.org/wp-content/uploads/2016/10/KS-Munster-Germany-Conf-2016.pdf.

AXYS, through its website and professional volunteers, can provide access to this report as well as additional information regarding peer-reviewed medical research, on-going clinical research, education and support.

47,XXY and Klinefelter syndrome are used as synonymous terms by medical professionals. The addition of the extra X chromosome often leads to characteristic, highly variable physical and medical findings and associated profiles of cognitive, developmental and neuropsychological findings.[6] Unlike other chromosomal disorders, such as Down syndrome, the physical features of KS are less distinct and more variable. While evidence of 47,XXY/KS may be present at birth, pronounced physical and medical characteristics usually do not manifest themselves until puberty and include: unusual height (approximately 3 inches taller than expected family history), low muscle tone (hypotonia), microorchidism (small testicles, an almost universal finding), very low testosterone levels, mild developmental delays (such as speech or motor development) or learning problems, widely spaced eyes (hypertelorism), hyper-extendable joints, flat feet, gynecomastia (male breast enlargement) and/or slow or incomplete pubertal

[4] Verri, et al., *supra* at note 2.

[5] Gravholt, et al., *supra* at note 2, p. 2; see also, Close S, Sadler L and Grey M, *In the Dark: Challenges of caring for sons with Klinefelter syndrome*, Journal of Pediatric Nursing, Vol. 31, Issue 1, pp. 11-20 (January-February 2016); see also, 2nd International Workshop on Klinefelter Syndrome, March 10-12, 2016, held in Muenster, Germany; https://genetic.org/wp-content/uploads/2016/10/KS-Muster-Germany-Conf-2016.pdf.

[6] Verri, et al., *supra* at note 2; see also Boda R, Januz J, Hutaff-Lee C, and Tataglia N, *The cognitive phenotype in Klinefelter syndrome: a review of literature including genetic and hormonal factors,* Developmental Disabilities Research Reviews, Vol. 15, No. 4, pp. 284-294 (2009). The latter publication contains a comprehensive review of literature on cognitive and neuropsychological studies in males with KS in childhood and adulthood, and discusses what is known about how hormonal and genetic factors influence cognitive features of males with 47,XXY/KS.

development as a result of testosterone deficiency.[7] Many, but not all, of the above symptoms are related to a nearly universal underlying condition in 47,XXY/KS males called hypergonadotropic hypogonadism. Hypergonadotropic hypogonadism refers to defective gonadal development or function of the gonads, resulting in elevated levels of gonadotropic hormones and inadequate levels of testosterone.

Why is Testosterone Important?

Contrary to popular belief (and ubiquitous television advertisements), low testosterone is not just a virility issue. As discussed earlier, males with 47,XXY/KS have testosterone levels which are lower than normal as a result of primary testicular failure[8]. Testosterone levels are determined by a blood test. Testosterone is a hormone, just like insulin (which is central to regulating fat and carbohydrate metabolism in our bodies and affects cognition and vascular compliance), and cortisol (a form of cortisone, which has major effects on our immune system, metabolism, mental functioning and bone formation). Testosterone is one of the steroid family of hormones, which are made in the adrenal glands, the testes and ovaries. A "steroid" means that it is in a class of hormones that are derived from the parent compound cholesterol. It is a hormone produced by both sexes and stimulates body growth and muscle and bone strength. In males, more than 90% of testosterone comes from the testes; however, 47,XXY/KS males almost universally have primary testicular failure. The resulting hormone imbalance typically manifests emotionally with mood disorders and cloudy, disorganized thinking and low energy as well as other physiologic symptoms.

KS/47,XXY Co-morbidities.

The fundamental premise for testosterone hormone replacement therapy ("HRT") is based on the fact that virtually all individuals who are 47,XXY/KS have hypergonadotropic hypogonadism, a progressive condition that leads to infertility and a significant testosterone deficit. Many endocrinologists mistakenly assume that an individual who is 47,XXY/KS does not need HRT if his testosterone levels are in the "low normal" range. Additional, more refined tests will determine beyond doubt that the 47,XXY/KS's body is demanding more testosterone and that the testes are incapable of producing it. Moreover, with age, the ability to produce testosterone will continue to decline. Ultimately, almost all organ systems are associated with an increased risk of morbidity and mortality.[9]

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[7] Verri, et al., *supra* at note 2; see also Tartaglia N, Wilson R, Bennet E, and Howell S, *Sex Chromosome Aneuploidies,* Handbook of Pediatric Neuropsychology, at pp. 805-811 (Springer Pub. Co. 2010).

[8] National Institutes of Health (http://.ghr.nlm.nih.gov/condition/Klinefelter-syndrome); Behr HM, Bergman M and Simoni M, *Chapter 6-Primary Testicular Failure*, (http://www.endotext.org.male/male6/male6.htm); Song S, Chiba K, Ramasamy R and Lamb D, *Recent advances in the genetics of testicular failure*, Asian Journal of Andrology, 2010: 18(3): 350-355.

[9] Swerdlow AJ, Higgins CD, Schoemaker MJ, Wright AF, Jacobs PA, *Mortality in Patients with Klinefelter syndrome in Britain: A Cohort Study,* Journal of Clinical Endocrinology & Metabolism, Vol. 90, No. 12, pp. 6516-6522 (December 1, 2005) (http://jcem.endojournals.org/content/90/12/6516.full).

The more notable health risks that have been associated with 47,XXY are listed below. Failure to employ HRT when indicated can put XXY individuals at risk for long-term health impacts and psychosocial difficulties:

- Osteoporosis and osteoporotic fractures. 20% of symptomatic vertebral fractures and 30% of hip fractures occur in men. Osteoporotic fractures in men are associated with substantial morbidity. One of the major secondary causes of osteoporosis in men is hypogonadism, which is found in up to 20% of men with symptomatic vertebral fractures and 50% of elderly men with hip fractures.[10]

- Significant reduction in muscle mass, including reduced muscle strength and maximum oxygen consumption is significantly reduced.[11]

- Breast cancer, mediastinal germ cell tumors (such as testicular cancer) and non-Hodgkin lymphoma.[12]

- Cardiovascular disease. Reduced androgen levels associated with hypogonadism or androgen deprivation therapy increase cardiovascular risk factors and produce marked adverse effects on cardiovascular function.[13]

- Cerebrovascular disease (commonly known as stroke).[14]

- Chronic leg ulceration.[15]

- Hypertension and significantly reduced systolic and diastolic function of the left ventricle. [16]

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[10] Ferlin A, Schipillit M, Di Mambro A, Vinanzi C, Fovesta C, *Osteoporosis in Klinefelter's syndrome,* Molecular Human Reproduction, Vol. 16, No. 6 (March 27, 2010).

[11] Bojesen A, Kristensenk K, Birkebaek NH, Feder J, Mosekilde L, Bennett P, Laurberg P, Frystyk J, Flyvbjerg A, Christiansen JS, Gravholt CH, *The Metabolic syndrome is Frequent in Klinefelter's Syndrome and Is Associated with Abdominal Obesity and Hypogonadism,* Diabetes Care, Vol. 29, No. 7, pp. 1591-8 (July 2006) http://care.diabetesjournals.org/content/29/7/1591; see also, Gravholt, et al., *supra* at note 2.

[12] The risk of breast cancer may exceed 200-fold that of karyotypically normal men. Swerdlow AJ, Schoemaker MJ, Higgins CD, Wright AF, Jacobs PA on behalf of the UK Clinical Cytogenics Group, *Cancer Incidence and Mortality in Men with Klinefelter Syndrome: A Cohort Study,* Journal of the National Cancer Institute, Vol. 97, No. 16, pp. 1204-1210 (August 17, 2005); Visootsak J and Graham JM, *Klinefelter syndrome and other sex chromosome aneuploidies,* Orphanet Journal of Rare Diseases, Vol. 1, No. 26 (October 26, 2006) (http://www.ojrd.com/content/1/1/42).

[13] Bojesen A and Gravholt CH, *Klinefelter syndrome in clinical practice,* Nature Clinic Practice Urology, Vol. 4, No. 4 (November 2006).

[14] Swerdlow, et al. *supra* at note 9.

[15] Swerdlow, et al. *supra* at note 9.

[16] Di Mambro A, Ferlin A, De Toni L, Selice R, Caretta N and Foresta C, *Endothelial progenitor cells as a new cardiovascular risk factor in Klinefelter's syndrome,* Molecular Human Reproduction, Vol. 16, No. 6, pp. 411-417 (February 2010).

- Autoimmune disorders, insulin resistance, Type 2 Diabetes, chronic autoimmune thyroiditis and lupus erythematosis.[17]

- Thrombosis.[18]

- Metabolic syndrome: There is a significant increase of the metabolic syndrome in 47,XXY/KS. This syndrome is characterized by a cluster of cardiovascular risk factors including increased central abdominal obesity, elevated triglycerides, reduced high-density lipoprotein, high blood pressure, increased fasting glucose, and hyperinsulinemia. Death rates in men with 47,XXY/KS higher compared to age-mates and their risk is 160% higher of developing metabolic syndrome [19]

- Chronic lung disease, such as chronic bronchitis, emphysema and asthma: it is possible that men with 47,XXY/KS suffer a higher incidence of lung cancer and COPD due to a lack of androgen action in the lungs and the resultant oxygen carrying capacity. There is also an increased incidence of smoking with 47,XXY/KS.[20]

- Obesity especially abdominal or truncal obesity. For men with 47,XXY/KS, the increased risk for obesity is 341% compared to age-matched men. Waist circumference, proxy for visceral adiposity men with low testosterone at baseline may be more at risk for developing visceral fat or central adiposity in later years (hall). An excess of 8% abdominal fat is found in men with 47,XXY/KS, Leptin, a biomarker of total amount of body fat, is elevated in 47,XXY/KS. Even the original photographs in Dr. Klinefelter's seminal paper in 1945 show abdominal obesity in the nine men studied.[21]

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[17] Bojesen, et al., *supra* at note 11; http://www.mayoclinic.com/health/klinefelter-syndrome/; see also, Gravholt, et al., *supra* at note 2.

[18] Swerdlow, et al., *supra* at note 9.

[19] Bojesen, et al., *supra* at note 13; Visootsak and Graham, *supra* at note 11; see also, Gravholt, et al., *supra* at note 2.

[20] Morales P, Furest I, Marco V, Macian V, Moreno B, Jimenez-Cruz JF, *Pathogenesis of the lung in restrictive defects of Klinefelter's syndrome,* Chest, Vol. 102, pp. 11550-1552 (1992) (http://chestjournal.chestpubs.org/content/102/5/1550); Swerdlow, et al., *supra a*t note 9.

[21] Bojesen A, Host C, Gravholt C, *Klinefelter's syndrome, type 2 diabetes and the metabolic syndrome: the impact of body composition.* Molecular Human Reproduction, Vo. 16, pp. 396-410 (2010) (http://dc357.4shared.com/doc/ILFz0Zn0/preview.html); Link J, Chen X, Arnold P and Reue K, *Metabolic impact of sex chromosomes*, Adipocyte, April 1, 2013;2(2); 74-79.

- Erectile Dysfunction. Testosterone deficiency is associated with a decline in erectile function and testosterone levels are inversely correlated with increasing severity of erectile dysfunction. Erectile dysfunction can be caused by multifactorial pathologies. In particular, erectile dysfunction may be the first symptom of cardiovascular disease.[22]

- Taurodontism (enlarged pulp chambers in the teeth and apical displacement of the bifurcation or trifurcation of roots, leading to dental decay).[23]

Recent research studies have demonstrated a serious lack of qualified and comprehensive medical care for 47,XXY/KS adults, with almost 40% reporting no medical follow up by a specialist and a strong need for multidisciplinary clinical care.[24]

Neurobiological and Neuropsychological Issues.

In addition to the medical/physical challenges that can be associated with KS, there are also strong neurobiological and psychological components that are often overlooked by many medical professionals.

Neuroanatomy of 47,XXY/KS Males

While the picture of 47,XXY/KS neuroanatomy is complex, magnetic resonance imaging and neuroimaging studies have found significant structural brain differences in males with 47,XXY/ KS that are consistent with the characteristic, but highly variable, intellectual and behavioral features of KS males[25] These studies have shown smaller total cerebral volume (consistent with smaller head size) and all lobular volumes (other than parietal white matter) and other neuroanatomical patterns that impact:

- Significant frontal-executive functioning deficits, referring to cognitive control processes involved in goal-directed behavior and problem solving, including problems with judgment, decision making,

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[22] Corona G, Petrone L, Paggi F, Lotti F, Boddi V, Fisher A, Vignozzi L, Balercia G, Sforza A, Forti, G, Mannucci E, Maggi M, *Sexual dysfunction in subjects with Klinefelter's syndrome.* International Journal of Andrology, Vol. 33, Issue 4, pp. 574-580 (August 2010).

[23] Jaspers MT and Witkop, Jr. CJ, *Taurodontism, an Isolated Trait Associated with Syndromes and X-Chromosomal Aneuploidy,* American Journal of Human Genetics, Vol. 32, pp. 396-413 (1980) (http://ncbi.nlm.nih.gov/pmc/articles/PMC1686063/).

[24] Skakkebaek, Anne et al, *Quality of Life in Men with Klinefelter Syndrome*, June, 2017.

[25] National Institutes of Health (http://www.ncbi.nlm.nih.gov/pubmed/17200249); Giedd JN, Clasen LS, Wallace GL, Lenroot RK, Lerch JP, Wells EM, Blumenthal JD, Nelson JE, Tossell JW, Stayer C, Evans AC, Samango-Sprouse CA, *XXY (Klinefelter syndrome): a Pediatric Quantitative Brain Magnetic Resonance Imaging Case-Control Study,* Pediatrics Vol. 119, No. 1 (January 1, 2007) (http://pediatrics.aapublications.org/content/119/1/e232.full); Itti E, Gaw Gonzalo IT, Pawlikowska-Haddal A, Boone KB, Mlikotic A, Itti L, et al., *The structural brain correlates of cognitive deficits in adults with Klinefelter syndrome,* The Journal of Clinical Endocrinology and Metabolism, Vol. 91, No. 4, pp. 1423-1427 (April 2006) (http://jcem.endojournals.org/content/91/4/1423.full); Itti E, Gaw Gonzolo I, Boone KB, Geschwind DH, Berman N, Pawlikowska-Haddal A, Itti L, Mishkin FS and Swerdloff RS, *Functional Neuroimaging Provides Evidence of Anomalous Cerebal Laterality in Adults with Klinefelter's syndrome,* Annals of Neurology, Vol. 54, pp. 699-673 (July 2003); see also, Gravholt, et al., *supra* at note 2.

poor inhibitory control organization, thought and planning, "with specific functions that include focused and sustained attention, holding thoughts in working memory, inhibiting irrelevant information and processing thoughts in a fluid and flexible way." (Thought to be related to smaller frontal and caudate volumes).[26]

- Impairment of planning and integration of motor movements, muscular weakness in the upper trunk and shoulders. (Thought to be related to the thinning of the motor cortex and the smaller frontal and caudate volumes).

- Language processing, reading, developmental and learning disabilities. (Thought to be related to cortical thinning in the superior region of the motor strip and abnormalities of the caudate nucleus).

- Mood, emotional modulation and social cognition. Elevated autistic traits have been observed in 47,XXY/KS males. (Thought to be related to reduced volumes in the insula, hippocampus and medial limbic system.[27]

Neuropsychological and Behavioral Features.

47,XXY/KS is characterized by a number of deficits in cognitive abilities (i.e., intelligence), language and executive functioning: some individuals with 47,XXY have established core features that do not cause significant problems and others demonstrate mild to moderate aberrant brain development and function.[28] The variability of the clinical neuropsychological and behavioral features associated with 47,XXY/KS is significant, but can include characteristic profiles of intellectual ability, motor impairments and rates of neurological and psychological disorder that are higher than those in the general population.[29] Some males have essentially no neuropsychological or behavioral concerns and go on to complete college degrees and training that produces successful careers. However, other adolescent males and men can have significant issues that produce difficult challenges for living independently. It is important to understand the genetic contributions to specific aspects of behavior and cognition of these affected males.[30]

[26] Gravholt, et al., *supra* at note 2, p. 26.

[27] Gravholt, et al., *supra* at note 2, p. 28; see also, Bryant DM, Hoeft F, Lai S, Lackey J, Roeltgen D, Ross J and Reiss AL, *Neuroanatomical Phenotype of Klinefelter syndrome in Childhood: A Voxel-Based Morphometry Study,* The Journal of Neuroscience, Vol. 31, No. 18, pp. 6654-6660 (May 4, 2011); Giedd, et al., *supra* at note 24; Tartaglia, et al., *supra* at note 6; Itti, et al., *supra* at note 24.

[28] Hong DS, Reis ALs, *Cognitive and neurological aspects of sex chromosome aneuploidies*, The Lancet Neurology, Vol. 13, No. 3, pp. 306-318 (March 2014); see also, Gravholt, et al. *supra* at note 2.

[29] Id.

[30] Id.

Cognitive

IQs for 47,XXY males can range from low to above average; however, overall mean cognitive abilities are generally found to be 5 to 10 points lower than the general population and siblings.[31] Cognitive abilities are the underlying brain-based skills that we need to carry out any task, from the simplest to the most complex. Cognitive abilities allow us to think, learn and remember.

Executive Function

Significant frontal-executive functioning deficits, which include issues with judgment, problem solving, decision making, memory, emotional self-regulation, concept formation, switching tasks, mental flexibility, problems with inhibitory skills (a prevalent issue), attention deficit disorder, impulse control disorder, short attention span, distractibility and poor organization.[32]

Learning Disabilities

Pervasive learning disabilities; verbal abilities and related language-based or reading deficits, such as dyslexia, verbal fluency, word retrieval, auditory processing and verbal memory, language comprehension and expression, and attentional deficits. These deficits cause children to fall behind in subjects where instruction is largely verbal based and as a result late adolescent 47,XXY/KS males can be several grade levels below their peers.[33]

Autism Spectrum Disorder; Psychological Disorders

Autism spectrum disorders and psychotic symptoms including paranoia, schizophrenia, delusional thinking and hallucinations have been observed; behavioral issues such as shyness, irritability, meltdowns, social withdrawal, depression and anxiety are higher in males with 47,XXY/KS than in the general population. It has been estimated that almost 60% of KS individuals will demonstrate some level of ADHD characteristics. These behavioral issues are also found in several other developmental disorders, such as autism. [34]

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[31] Tartaglia, et al., *supra* at note 6; Verri, et al., *supra* at note 2.

[32] Geschwind D and Dykens E, *Neurobehavioral and Psychosocial Issues in Klinefelter syndrome,* Learning Disabilities Research & Practice, Vol. 19, No. 3, pp. 166-173 (June 2004); Boone KB, Swerdloff RS, Miller BL, et al., *Neuropsychological profiles of adults with Klinefelter syndrome*, Journal of International Neuropsychological Society, pp. 446-456 (2001); see also Verri, et al., *supra* at note 2 and Tartaglia, et al., *supra* at note 6.

[33] Geschwind and Dykens, *supra* at note 31; see also, Gravholt, et al., *supra* at note 2.

[34] Turriff A, Levey HP and Biesecker B, *Prevalence and Psychosocial Correlates of Depressive Symptoms among Adolescents and Adults with Klinefelter syndrome,* Genetics in Medicine Vol. 13, No. 11, pp. 966-972 (November 2001 (http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3208082/?tool=pubmed); Bruining H, Swaab H, Kas M and van Engeland H, *Psychiatric characteristics in a self-selected sample of boys with Klinefelter syndrome.* Pediatrics, Vol. 123, No. 5, pp. 865-870 (May 1, 2009) (http://pediatrics.aapublications.org.content/123/5/e865.long); van Rijn S, Aleman A, Swaab H and Kahn R, *Klinefelter's syndrome (karotype 47, XXY) and schizophrenia-spectrum pathology,* The British Journal of Psychiatry, Vol. 189, pp. 459-461 (2006) (http://bjp.rcpsych.org/content/189/5/459.full); Zijlstra R, Bierman M, Swaab H and van Rijn S, *Role of the X Chromosome in social Behavioral Dysfunction and autism-*

These deficits persist into adulthood.[35] There has also been recent research (discussed below) that shows the brain areas that process emotional interpretation in some 47,XXY/KS individuals have a different anatomical structure than the norm. This could be the reason that some 47,XXY/KS individuals have difficulty interpreting social cues and may react, or appear to be under-reacting, to emotional situations. With speech and language challenges (again, associated with their neuroanatomy) they may also have difficulty verbalizing their feelings. This can often be misinterpreted by people not familiar with the condition (including police, prosecutors, judges, psychologists, etc.) as the person not being concerned or remorseful because their physical appearance remains unexpressive and they are not able to articulate how they feel. This can sometimes lead to harsher or more significant penalties.

What Role Does Genetics Evidence Play in the Criminal Justice System?

Most, if not all, reported cases dealing with genetic evidence in criminal law involve genetic conditions which are inherited, which is not true with 47,XXY/KS, and do not deal with the broader issue of the role of genetics evidence in the criminal justice system. The use of genetics evidence has fallen into two main categories, defense and mitigation, and focus on a genetic predisposition to criminal behavior rather than the existence of a scientifically proven genetic abnormality (such as is the case with 47,XXY/KS) and its behavioral and cognitive traits and deficits. As previously stated, there is no evidence that a male diagnosed with 47, XXY/KS is predisposed to criminal activity or is more likely to engage in criminal behavior. However, the severity of the aspects of 47,XXY/KS which is exhibited by an individual who has been charged with a crime is an important factor in assessing culpability and as a mitigating factor.

While 47,XXY/KS is not a prima facie defense in any case, AXYS does believe that it can be a substantially mitigating factor in an individual's defense and should be taken into account by the court in sentencing. A number of factors which are present in 47,XXY/KS can contribute to poor judgment and impulsive behaviors that can contribute to the risk of criminal behavior:

- Executive function problems frequently manifest as impulse control problems, poor judgment and inappropriate emotional outbursts. There is often a failure to learn from prior adverse experiences or outcomes. As one researcher reported, "weak inhibitory control can lead to impulsive behaviors and acting without taking into account the associated risks and consequences of the action."[36] (None of these things typically lead to serious misbehaviors, but when provoked by others or tempted by opportunities, 47,XXY/KS individuals may make poor choices. Immaturity may lead a young adult to behave more like a rebellious adolescent. And when faced with an authority figure, for example a police officer, they may have an outburst or "meltdown" rather than recognize the risk of the situation and behave accordingly. Additionally, because of the existence and impact of executive functioning deficits, verbal processing deficits and other 47,XXY/KS-associated issues discussed in this paper, a 47,XXY/KS male may not

like Behavior, European Psychiatric Review, Vol. 3, No. 1, pp. 47-50 (2010); *see also* Geschwind and Dykens, *supra* at note 31; Verri, et al., *supra* at note 2.

[35] Geschwind and Dykens, *supra* at note 31; Verri, et al., *supra* at note 2; Tartaglia, et al., *supra* at note 6.

[36] vanRijn, S and Swaab, H, *Executive Function and the Relationship with Behavior Problems in Children with 47,XXY and 47,XXX, Genes, Brain and Behavior* (2015) 14:pg 206.

understand his *Miranda* rights when they are read or otherwise presented to him by law enforcement officers and may not know how to protect those rights (such as invoking the Constitutional right to remain silent).

- Delayed social development: many of those who are 47,XXY/KS experience social delays that can put them at risk—especially in the critical years transitioning from adolescence to adulthood. It is not uncommon for young adults who are 47,XXY to persist in juvenile behaviors and on-line games. They may seek out social peers who are 5 to 10 years younger than they are because their social maturity may be 6-8 years delayed behind their chronological age. Many have a natural attraction to girls who are significantly younger simply because these girls are their social peers. This can present major risk factors for a 22 or 23 year old male interacting with a 14 to 16 year old female.

- Auditory processing deficiencies are prevalent, and the 47,XXY/KS individual may have difficulty understanding or processing all of the social innuendos in what is being said to him.

- Communication deficits are prevalent. A recent study in the Netherlands showed that many 47,XXY/KS individuals struggle to interpret facial expressions.[37] For example, they struggle to distinguish between anger and sadness. This inability to pick up on the nuance of communication puts them at a significant disadvantage in challenging social situations. They can be emotionally isolated and unable to empathize with others, because they don't fully grasp the other person's point of view.

- Bullying by others is prevalent. This abuse puts them on the defensive, and it often injects them into the spotlight when they respond to bullies. As seen above, being the focus of what they perceive as unjust attention from authorities may provoke inappropriate behaviors. Also, in an effort to seek refuge from or please a bully to get the bullying to stop, 47,XXY/KS individuals may impulsively seek out support from others who may be able to fend off the bullies. In some cases, these so-called friends may further exploit or abuse the 47,XXY/KS individual.

- Social behavior and social cognition: Ongoing research into the relationship between brain structure and function and areas involved with social behavior is helping us understand why some 47,XXY/KS individuals can struggle with perception, reasoning, attention and decision-making while appearing to have normal intellectual functioning. Many 47,XXY/KS individuals have characteristics and behaviors that will place them on the autism spectrum disorder spectrum (ASD) where general intellectual functioning can be disassociated from social behavior and social function in very dramatic ways. In particular, impulsive behavior has been shown to be associated with a decoupling of prefrontal and subcortical networks[38] which has been demonstrated in a number of 47,XXY/KS research studies. In more simple terms, some 47,XXY/KS individuals can appear to be intelligent, capable, goal-directed and responsible but at the same time have significant challenges with consistent decision-making and impulsivity that is related to impaired neurobiological development.

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[37] See van Rijn, et al., *supra* at note 33.

[38] Kennedy, Daniel P, Adolphs, Ralph, *"The Social Brain in Psychiatric and Neurological Disorders",* Trends Cogn. Sci. 2012 Nov; 16(11): 559–572. http://conte.caltech.edu/sites/default/files/publications/TICS_Kennedy.pdf.

- Age-appropriate sexual interactions. This seems to be a particularly difficult area for many reasons. The mis-match between chronological age and actual maturational age; the difficulty with communication and emotional intelligence; the perception they are responsible, functional adults; executive decision-making deficits; fluctuations in testosterone levels if receiving hormone replacement therapy; learning challenges and more. If there is one area that makes some 47,XXY/KS individuals highly at risk for inappropriate behavior and subsequent severe legal punishments, it would be this area. They have been dealt a genetic hand that is the equivalent of a perfect storm of potential disaster. There are a number of books that have been written about this subject and current research is being conducted that will help further explain the significant risk 47,XXY/KS adults have in this area.

Summary.

In summary, the following issues should be considered with a 47,XXY/KS individual that may be experiencing difficulty that involves the criminal justice system:

- 47,XXY/KS is a genetic condition that can have numerous medical, social, emotional, psychological and behavioral implications.
- Outside of a small number of trained and experienced health professionals, it is a condition that is not well-understood by the general medical community.
- 47,XXY/KS individuals, especially adults, should be considered a vulnerable population that may need special support and advocacy when involved with the criminal justice system. Parents and other family members may not always be aware of or understand the need for special advocacy.
- Treatment and special support, as opposed to incarceration, are more appropriate responses than punitive consequences for 47,XXY/KS individuals needing help with managing behavior.

Please contact the AXYS organization for suggestions on additional research resources that may be pertinent to any specific criminal justice situation. There are also several excellent publications to learn more about Klinefelter syndrome[39] and legal defense strategies for individuals with executive function challenges.[40]

www.axysgenetic.org or info@genetic.org or 1-888-999-9428

[39] *Living with Klinefelter Syndrome* (47,XXY), Trisomy X (47,XXX) and 47,XYY: A guide for families and individuals affected by X and Y chromosome variations (2012), Virginia Isaacs Cover MSW; available at www.genetic.org/books.

[40] *Disorders of Executive Functions, Civil and Criminal Law Applications* (1998), Harold V. Hall and Robert J. Sbordone.