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5p Deletions: Current Knowledge and Future Directions

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Abstract

Disorders resulting from 5p deletions (5p–) were first recognized by Lejeune et al. in 1963 [Lejeune et al. (1963); C R Hebd Seances Acad Sci 257:3098-3102]. 5p– is caused by partial or total deletion of the short arm of chromosome 5. The most recognizable phenotype is characterized by a high-pitched cry, dysmorphic features, poor growth, and developmental delay. This report reviews 5p– disorders and their molecular basis. Hemizygosity for genes located within this region have been implicated in contributing to the phenotype. A review of the genes on 5p which may be dosage sensitive is summarized. Because of the growing knowledge of these specific genes, future directions to explore potential targeted therapies for individuals with 5p– are discussed.

Keywords

Cri du Chat syndrome; 5p deletion syndrome; 5p minus syndrome; natural history; hemizygosity; haploinsufficiency

INTRODUCTION

Individuals with 5p deletions (or 5p minus, 5p–) were initially described as having Cri du Chat syndrome in 1963 by Lejeune et al. With an incidence of 1 in 15,000 to 1 in 50,000 live births, it is suggested to be one of the most common contiguous gene deletion disorders [Niebuhr, 1978; Higurashi et al., 1990]. Although the classic 5p– phenotype including a characteristic cry, dysmorphic features, growth, and developmental delays is the predominant disorder for individuals with 5p deletions, there is a wide spectrum of features. 5p deletions, whether terminal or interstitial, occur at different breakpoints. Hence, the variability seen among individuals may be attributed to the differences in their genotypes.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of this article at the publisher's web-site.

Hence, the variability seen among individuals may be attributed to the differences in their genotypes.

The various genes that may be contributing to an affected individual's condition as a result of their hemizygosity are discussed. This information is anticipated to continually change given the exponential rate of discoveries in genetics. It is important to identify these genes, further characterize their consequences in 5p–, and translate this knowledge into treatment. During the current era of genomic medicine, we are no longer restricted to pooling all affected individuals with 5p deletions and then speculating on the severity of their features and outcomes. Rather, we now have the ability to classify each individual based on the genes affected by their specific deletion. This allows for the opportunity to personalize clinical care, anticipatory guidance, management, and prognosis. Understanding the molecular basis of the condition is fundamental for progressing toward the goal of treatment for haploinsufficiency resulting from 5p hemizygosity.

5P MINUS FAMILY DATABASE

Analyses from the 5p Minus Family Database, which includes clinical information as well as extensive educational and developmental evaluations of a cohort of 286 individuals with 5p deletions, are reported (Unpublished, DJC). The cohort is comprised of participants in the 5p Minus Society, an online family support group in the United States for individuals with 5p deletions. All data are based on parent reports. The 5p Minus Society's Professional Advisory Board, which is comprised of medical professionals familiar with 5p deletions, created a questionnaire in 1999. Upon completion of the paper questionnaire, results were entered into the database by the 5p Minus Society director. In 2012, the database was transferred to the 5p Minus Society's Professional Advisory Board chair with IRB approval to continue data collection. We present data on 286 individuals, of whom 59% are female. The average age of the proband when the questionnaires were completed is 12 years, with a range of 4 months to 29 years. The 5p Minus Society also maintains a separate database of 1,500 members which allows families the option to have their contact information shared with other members or remain confidential. This directory is maintained by the society's executive director. Because the 5p Minus Family Database does not have high resolution copy number data for each individual registered, the clinical characteristics discussed below relate to that of the overall 5p deletion population.

MOLECULAR CHARACTERIZATION

5p deletions can be interstitial or terminal and range from 560 kb to 40 Mb in size [Simmons et al., 1995; Gu et al., 2013; Elmakky et al., 2014]. However, because their cohort did not have any terminal deletions greater than 33 Mb, Zhang et al. [2005] speculated that those monosomies may not be compatible with life. 5p deletions are most commonly de novo occurrences, which are paternal in origin in 80–90% of cases, possibly arising from chromosome breakage during gamete formation in males [Overhauser et al., 1990; Mainardi et al., 2001]. Ten to 15% are the result of an unbalanced parental translocation [Mainardi et al., 2006]. Terminal deletions comprise 80–90% of cases and interstitial deletions account for 3–5% [Mainardi et al., 2006]. Less common mechanisms include mosaicism (1.4%), inversions (0.5%), or ring chromosomes (0.5%) [Perfumo et al., 2000].

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Although many individuals have similar breakpoints, there is no common recurring breakpoint [Mainardi et al., 2001]. Studies differ on the correlation between deletion size and severity of clinical features. Variations ranged from finding no relationship [Marinescu et al., 1999] to observing a correlation between the clinical severity and the increasing size of deletion [Wilkins et al., 1983; Mainardi et al., 2001]. When available, critical regions for specific symptoms are listed as well as depicted in Figure 1 [Overhauser et al., 1986; Hand et al., 2000; Kondoh et al., 2005; Wu et al., 2005; Zhang et al., 2005; Gu et al., 2013; Elmakky et al., 2014]. Although individuals with varying phenotypes had apparently similar breakpoints, some studies were limited by the use of older cytogenetic techniques. Because of this limitation, some previous reports with phenotypic maps could not be depicted here and were not included [Church et al., 1995, 1997; Gersh et al., 1995].

There is also phenotypic heterogeneity among family members with the same deletion [Walker et al., 1984; Church et al., 1995; Cornish et al., 1999; Fang et al., 2008]. There are parents of affected children with 5p– deletions who themselves have the same deletion yet do not appear to have any symptoms [Gersh et al., 1994]. Furthermore, siblings born to these parents, despite having inherited the same deletion, vary with respect to features such as growth and development [Church et al., 1995]. The effects of modifier genes, additional copy number variants, mutations or allelic variation in the homologous allele, occult duplications, epigenetic modifications, coexisting diagnoses, variable expressivity, or environmental factors have not been explored. No imprinted genes have been identified. However, members of families in which the deletion was maternally inherited were observed to have only mild growth and developmental delays versus families in whom it was paternally inherited [Bengtsson et al., 1990; Gersh et al., 1994; Luthardt et al., 1995; Johnson et al., 2000]. If there are de novo cases with the same breakpoints, a comparison analysis of those whose hemizygous alleles are paternal versus maternal in origin may elucidate whether phenotypic differences exist.

CLINICAL CHARACTERIZATION

Dysmorphology

Historically, infants suspected as having 5p– upon recognizing their high-pitched cry were subsequently confirmed by cytogenetic analysis. Currently, genotyping is obtained for numerous medical indications, a practice that results in the identification of 5p– first, followed by clinical characterization, which broadens the phenotypic spectrum. Because it is a unique and easily identifiable feature, the monotonous cry has been well studied. Multiple critical regions have been reported for the characteristic cry, including a 640 kb region between 6,365,349 and 7,003,686 [Wu et al., 2005] and a 1.7 Mb region between 5,791,886 and 7,539,901 [Zhang et al., 2005]. The cry has also been included with other features in a 5.4 Mb region between 10,361,807 and 15,728,105 [Kondoh et al., 2005] and a 5.5 Mb

region between 22,178 and 5,539,182 (Fig. 1) [Elmakky et al., 2014]. However, not all affected individuals have this distinctive feature.

Individuals with 5p deletions may have dysmorphic features such as microcephaly, round facies, hypertelorism, epicanthal folds, downslanting palpebral fissures, broad nasal bridge, low-set ears, preauricular tags, down-turned corners of the mouth, short neck, micrognathia, and dental mal-occlusion (Fig. 2) [Niebuhr, 1978; Wilkins et al., 1980, 1983; Carlin, 1990; Mainardi, 2006]. Dysmorphic facial features become less striking with age (Fig. 2) [Van Buggenhout et al., 2000]. Facial dysmorphology has been narrowed to a 2.6 Mb region between 8,939,505 and 11,588,196 [Zhang et al., 2005]. Kondoh et al. [2005] report an 8.3 Mb region between 1 and 8,268,512 associated with epicanthal folds and a 5.4 Mb region between 10,361,807 and 15,728,105 associated with microcephaly, micrognathia, hypertelorism, and a high palate. Microcephaly and other dysmorphic facies were reported in the 5.5 Mb region reported by Elmakky et al. [2014] (Fig. 1). Individuals may also have single transverse palmar creases, short metacarpals, clinodactyly, syndactyly, and/or pes planus.

Hearing

Conductive hearing loss may occur in children due to chronic otitis media infections. Sensorineural hearing loss has also been reported. The 5p Minus Family Database indicates that 15% of children had tympanostomy tubes placed (as compared to 1.3% among the general pediatric population in the United States [Bright et al., 1993]) and 8.4% had hearing loss (as compared to 0.37% who are born with hearing loss in the United States [Mason et al., 2008]). Hearing loss may present as frustration, aggression, inconsistency in responding to directions, difficulty with language, and speech, as well as immature social interactions. Many children benefit from hearing aids. Thus, appropriate treatments for infections as well as audiological evaluations are an important component of management and surveillance among children with 5p–. There is also a high incidence of hyperacusis in 70–80% of children with 5p– as compared to 3.2% among children in the general population [Coelho et al., 2007]. This over-sensitivity to sounds can manifest as severe agitation, distress, or being easily startled.

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Vision

The 5p Minus Family Database indicates that 46% have ophthalmologic findings. Vision abnormalities that are prevalent among individuals with 5p– include myopia (15%), strabismus (45–53%), cataracts (2%), and optic nerve abnormalities (5–19%) [Niebuhr, 1978; Mainardi et al., 2006]. A 4.2 Mb region between 21,911,081 and 26,132,545 has been associated with strabismus (Fig. 1) [Kondoh et al., 2005].

Additional Conditions

Prenatal and postnatal growth deficiency is common (52–70%) and continues life long, for which specific growth charts are available [Marinescu et al., 2000]. The endocrinologic basis for this has not been well characterized. Poor feeding (44%), constipation (24%), hypotonia (72%), respiratory tract infections (52%), and scoliosis (43%) occur frequently in individuals with 5p– [Niebuhr, 1978; Mainardi et al., 2006]. Growth deficiency and hypotonia were included in the 8.3 Mb region between 1 and 8,268,412 reported by Kondoh et al. [2005]. Hypotonia and feeding difficulties were also reported in the 5.5 Mb deletion reported by Elmakky et al. [2014] (Fig. 1). Up to 30% of individuals with 5p– have brain findings such as hypoplasia or agenesis of the corpus callosum, periventricular leukomalacia, abnormalities of white matter myelination, cerebral and/or cerebellar atrophy, or hydrocephalus [Mainardi et al., 2006]. Cardiovascular (18–36%), gastrointestinal (4–21%), renal (6–18%), and genitourinary anomalies (4–21%) may also occur as further detailed by Mainardi et al. [2006]. Kondoh et al. [2005] identified a 3.6 Mb region between 17,770,293 and 21,394,873 associated with congenital heart defects and a 4.2 Mb region between 21,911,081 and 26,132,545 associated with renal anomalies (Fig. 1).

Behavior

Over 80–90% of children with 5p– have hyperactivity, with 70% displaying clinical features of attention deficit hyperactivity disorder (ADHD) (Dykens and Clarke, 1997; Cornish and Munir, 1998]. Other common behaviors include impulsiveness, frustration, stubbornness, temper tantrums, obsessive-compulsive disorder, poor concentration, clumsiness, aggressive behaviors, such as biting, hair pulling, pinching, and hitting, and self-injurious behaviors such as self-biting, head-banging, scratching, rubbing, and skin-picking [Collins and Cornish, 2002]. Individuals may have characteristics of autism spectrum disorders (ASDs) such as hand flapping, obsessive attachments to objects, twirling objects, repetitive movements, and rocking. Behaviors can escalate due to pain, constipation, vision, or hearing deficits. No gender differences for maladaptive behaviors have been reported in the 5p Minus Family Database.

Communication

Speech delay has been associated with a 3.2 Mb region between 3,021,203 and 6,412,938 [Zhang et al., 2005] and included in the 5.5 Mb deletion reported by Elmakky et al. [2014] (Fig. 1). Despite their speech delays, children with 5p– are able to communicate their needs and socially interact with others [Cornish and Pigram, 1996]. They have better receptive than expressive language [Cornish and Munir, 1998]. Early stimulation, speech therapy, and alternatives such as sign language or communication devices are effective means of developing communication skills, with 50% of children capable of communicating via sign language.

Development

Into the 1960s, individuals with significant disabilities, including those with 5p–, were commonly placed into institutions [Gellis and Feingold, 1969]. Consequently, early empirical exploration of 5p– consisted of studies of individuals who often did not have

access to family, education, or systematic medical care, which resulted in a pessimistic prognosis. It is recognized that infant intervention, early education, and home-rearing improve prognosis [Wilkins et al., 1980, 1983; Carlin, 1990]. The 5p Minus Family Database showed that those who had early intervention sat up on average 8 months earlier, walked independently 2 months earlier, dressed themselves 17 months earlier, and were toilet-trained 13 months earlier than those children who received no interventions. Physical and occupational therapy facilitate progression of skills. The average ages reported for reaching developmental milestones were: sitting up at 14 months, walking alone at 43 months, dressing at 78 months, and toilet-training at 90 months. Gait problems were included in the 5.4 Mb region between 10,361,807 and 15,728,105 reported by Kondoh et al. [2005] (Fig. 1).

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Consequences of 5p– also include varying degrees of intellectual disability ranging from mild to profound, and there are some individuals with apparently normal intellectual function. Although intellectual disability has been difficult to confine to a genomic location, this feature has been associated with multiple critical regions, including a 1.2 Mb region between 7,392,488 and 9,714,368, an 8.9 Mb region between 9,460,963 and 31,996,577, a 13.8 Mb region between 18,190,397 and 31,996,577 [Zhang et al., 2005], and a 540 kb region between 16,570,363 and 17,108,840 (Fig. 1) [Kondoh et al., 2005].

Adulthood

Children with 5p– undergo puberty at typical ages. Two of six (33%) adolescent and adult males were found to have small testes (Breg et al., 1970). Individuals may have premature graying of hair beginning as early as 15 years of age. Sleep disturbances continue from childhood into adulthood and may worsen with age. Constipation remains a significant problem throughout adulthood. Determinations of the etiology and best practice management for constipation in 5p– have not been reported. Of the 70–80% of adults with hyperacusis, the disorder progresses to include more sound ranges and pitches. Long-term studies are needed to quantify outcomes in adults with 5p– such as their ability to be gainfully employed or live independently.

Life Expectancy

Early observations of 5p– reported that death occurred in childhood in 32 of 341 individuals (9.7%) [Niebuhr, 1978], but this rate is decreasing (6.4%) [Mainardi et al., 2006]. Of those who died, 75% (24/32) died in the first few months of life and 90% (29/32) did so within the first year [Niebuhr, 1978]. However, in more recent studies, these rates are lower with 36% of deaths in the first month of life and 64% in the first year of life [Mainardi et al., 2006]. Pneumonia, congenital heart defects, and respiratory distress syndrome are the most common causes of death. Those with unbalanced translocations that include a 5p deletion have a higher mortality rate (18.5%) than those with terminal deletions (4.8%) [Mainardi et al., 2006]. If no major organ defects or other critical medical conditions exist, life

expectancy appears to be normal. The oldest person in the 5p Minus Database is 64 years of age.

Management

Surveillance and management is largely symptomatic and based on standard treatments for any associated conditions. Further development of practical guidelines for the management of individuals with 5p– is needed, as they are available for other contiguous gene deletion disorders [Battaglia et al., 2008; Bassett et al., 2011].

5p Deletions With No Apparent Phenotype

Despite being the fifth largest chromosome, chromosome 5 is very gene poor [Schmutz et al., 2004] and there are people with 5p deletions who are apparently normal. Terminal deletions at 1–4,500,000 were found to have no phenotypic effects [Bengtsson et al., 1990]. Gu et al. [2013] reported a female with three small interstitial deletions at 4,200,304–7,081,712 (2.9 Mb), 23,642,864–24,156,987 (510 kb), and 27,332,938–30,493,484 (3.2 Mb) who had no discernable phenotype. Zhang et al. [2005] observed a person with no phenotype who had a 13.8 Mb deletion between 18,226,154 and 32,032,334. Overhauser et al. [1986] and Hand et al. [2000] described multi-generational families transmitting a 10.8 Mb deletion between 18,500,001 and 29,300,000 who were apparently normal. However, Johnson et al. [2000] identified microcephaly, seizures, and developmental delay, while Mainardi et al. [2001] noted dysmorphic features and developmental delay among individuals with deletions within the same region.

5p Deletions With Unmasked Recessive Conditions

Individuals with 5p– are at risk for recessive conditions if a gene harbors a mutation in the single copy that is present. Although such a mutation may only account for a small subgroup of individuals with 5p–, it still may be a contributing factor to variations in phenotype despite similar deletion sizes. For example, primary ciliary dyskinesia (PCD) is associated with frequent infections such as sinusitis, otitis media, pneumonia, as well as respiratory distress in newborns and infertility. PCD is an autosomal recessive disorder caused by mutations in the dynein axonemal heavy chain 5 (*DNAH5*) gene (13,690,437– 3,944,589) which results in ciliary dysmotility. Because *DNAH5* is located on 5p, individuals with 5p deletions in trans with a *DNAH5* mutation have been affected with PCD [Shapiro et al., 2014]. Identification of PCD and other autosomal recessive conditions in 5p are thus important for specialized management and clinical care.

CHROMOSOME 5P GENE DOSAGE MAP

Loss of several genes in the 5p region contributes to the phenotype. The mechanism of haploinsufficiency has been implicated for many disorders and prediction models have been developed to help interpret whether gene loss leads to disease [Huang et al., 2010]. All genes were reviewed using the February 2009 assembly in the genomic location of 1–48,000,000, which includes the cytogenetic location of 5p15.33 to 5p11. Literature searches for information on genes without OMIM (Online Mendelian Inheritance in Man, www.omim.org) entries were performed through PubMed (www.ncbi.nlm.nih.gov/pubmed).

Dosage effects of 314 genes were analyzed by methods as discussed in Cody et al. [2009]. Thirty-seven genes (12%) were classified as dosage insensitive [Supplementary Table SI—see supporting information online]; five genes (1.6%) were classified as dosage sensitive leading to haploinsufficiency (*TERT, SEMA5A, MARCH6, CTNND2, NPR3*); six genes (1.9%) have effects that are conditionally haploinsufficient and depend on another genetic or environmental factor to cause an abnormal phenotype (*SLC6A3, CDH18, CDH12, CDH10, CDH9, CDH6*); and two genes (0.6%) have effects that are haplolethal (*RICTOR, DAB2;* Table I). There was insufficient information to classify 264 genes.

DOSAGE SENSITIVE GENES: HAPLOINSUFFICIENT

TERT (1,253,281–1,295,177): Accelerated Telomere Shortening

Hemizygosity of *TERT* has been implicated in the dysfunction of telomere-length maintenance and sustained cell proliferation in both mouse embryonic stem cells heterozygous for *TERT* disruption [Liu et al., 2002] and human cell lines derived from people with 5p– and subsequent *TERT* deletions [Zhang et al., 2003]. Reconstitution of telomerase activity has been demonstrated to improve telomere length. Zhang et al. [2003] detected a heterozygous deletion of *TERT* in 10/10 people with 5p– and posited that the resulting shortened telomeres may be responsible for features such as premature graying of the hair or small testes. Du et al. [2007] also reported that telomere length, while within the normal range, was significantly shorter in a cohort of 41 individuals with 5p– and subsequent *TERT* deletions compared to normal controls. The shortening was more significant in older individuals, suggesting an age-dependent acceleration of truncation. An additional three individuals in their cohort had two intact copies of *TERT*. Fourteen individuals had fingernail ridging and 10 had early graying of the hair; however, these phenotypic features did not correlate with telomere length. In addition, one individual with fingernail ridging had two intact copies of *TERT*, making it unlikely for *TERT* to be responsible for this feature.

Heterozygous mutations in *TERT* have also been implicated in autosomal dominant dyskeratosis congenita (DC), a rare inherited bone marrow failure syndrome whose early features include fingernail ridging and early graying of the hair. Genetic anticipation is seen among families with DC and is thought to be due to the progressive shortening of telomeres through subsequent generations, with DC manifestations occurring when telomeres reach a critically short length. Telomere lengths of people with DC were significantly shorter than those in people with 5p– and subsequent *TERT* deletions [Du et al., 2007]. These results suggest that individuals with de novo *TERT* deletions, common in cases of 5p–, would only have slightly shortened telomeres after one generation, and therefore not be at risk for the severe manifestations of DC. However, progressive telomere shortening could put subsequent generations at risk and may explain the increased severity of symptoms seen between some parent-child pairs with 5p– [Gersh et al., 1994]. Further studies are needed to quantify this risk and determine whether it will be a future health concern for families.

SEMA5A (SEMAF) (9,035,137–9,546,232): ASDs

Hemizygosity of *SEMA5A* may disrupt normal brain development in individuals with 5p–, leading to ASDs and possibly to other cognitive deficits [Simmons et al., 1998; Weiss et al., 2009; Duan et al., 2014]. Simmons et al. [1998] postulated that the pattern of expression of Sema5A in the developing mouse brain implicated the gene in neuronal migration, and its dysfunction could lead to the developmental delay, intellectual disability, and/or microcephaly seen in people with 5p–. However, further studies are needed to support or refute this hypothesis. Sema5A homozygous knockout (KO) mice have an increased number of excitatory synapses in dentate granule cells and higher amplitudes and frequencies of the signals that pass through excitatory synapses. In behavioral studies, these mice displayed altered patterns of social interaction compared to control animals, being less willing to interact with unfamiliar mice. No significant deficits were reported in heterozygous KO mice [Duan et al., 2014]. Weiss et al. [2009] demonstrated that there is also reduced expression of *SEMA5A* in people with ASDs. Because imbalances of excitatory and inhibitory synapses have been associated with neurodevelopmental disorders such as ASDs [Penzes et al., 2011], these data are consistent with the increased incidence of ASDs associated with *SEMA5A* hemizygosity.

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MARCH6 (TEB4) (10,353,750–10,440,499): High-Pitched Cry

Hemizygosity of *MARCH6*, which encodes a conserved E3 ubiquitin-conjugating enzyme ligase, may play a role in the high-pitched cry of individuals with 5p– [Wu et al., 2005]. *MARCH6* is a member of the same ubiquitin-conjugating degradation pathway as another candidate gene for this role, the UBC-E2 homolog *FLJ25076* (6,437,347–6,496,721). *FLJ25076* is highly expressed in the scalp and thoracic tissues, and has also been observed in the brain, neck, skeletal muscle, arm, and adrenal gland. *FLJ25076* is thought to be involved in protein degradation, and its expression in the scalp suggests a possible role in the development of facial features [Wu et al., 2005]. The presence of two 5p– genes in the same pathway demonstrates that multiple genes are likely implicated in causing a similar end effect on phenotype and explains why multiple critical regions in 5p have been identified for the high-pitched cry and other features [Church et al., 1995; Kondoh et al., 2005; Wu et al., 2005; Zhang et al., 2005].

CTNND2 (10,971,951–11,904,154): Intellectual Disability

Individuals with 5p– were found to have severe intellectual disability when the deleted hemizygous region included loss of *CTNND2* [Medina et al., 2000]. In addition, individuals with heterozygous loss of exclusively *CTNND2* via micro-deletion, intragenic deletion, or disruption by balanced translocation have been described to have mild intellectual disabilities with or without reading problems [Hofmeister et al., 2015], autistic traits

[Asadollahi et al., 2014], and developmental delay [Belcaro et al., 2015]. One individual with 5p– has a mild cognitive and behavioral phenotype due to a complex rearrangement that resulted in a partial duplication (11,419,020–12,969,933; *CTNND2* exons 1–14) and a partial deletion (113,576–11,419,020; *CTNND2* exons 15–68) with one breakpoint within *CTNND2*. Because the promoter region lies within the duplicated portion of *CTNND2*, it is possible that the partial preservation of *CTNND2* ameliorated the severity of this individual's cognitive phenotype [Sardina et al., 2014].

CTNND2 is expressed early in neurons in the developing nervous system and is thought to play a role in neuronal migration. Matter et al. [2009] reported on the dendritic complexity, spine density, and cortical responsiveness to visual stimulation of Ctnnd2 homozygous KO mice. These measures were normal between KO and control mice at 5 weeks of age, but decreased spine density and stability and subsequent deficits were observed in the KO group at 10 weeks. Others report an increase of spine and synaptic density in null mice, suggesting that Ctnnd2 is important in the overall maintenance and stability of dendritic structures [Yuan et al., 2013, 2015]. Furthermore, Yuan et al. [2013] report that the expression of Mef2 in rat neurons with knockdown of Ctnnd2 in cell culture eliminates excess neuronal spines, providing a potential therapeutic mechanism for *CTNND2* hemizygosity.

NPR3 (GC-A) (32,710,283–32,791,829): Essential Hypertension

Deletions of *NPR3* have been implicated in salt-resistant essential hypertension in mouse models. Both heterozygous and homozygous KO mice were found to have significantly elevated blood pressures, independent of salt intake, when compared to wild-type [Lopez et al., 1995], which suggests a dosage sensitive effect. However, further studies are needed to determine if these effects are also seen in humans with *NPR3* hemizygosity. Currently, there are no reports that adults with 5p– have increased rates of hypertension; however, further natural history data are needed, as this finding would be important to consider when developing surveillance guidelines.

DOSAGE SENSITIVE GENES: CONDITIONALLY HAPLOINSUFFICIENT

SLC6A3 (DAT1) (1,392,904–1,445,542): ADHD

SLC6A3, which encodes the dopamine transporter (DAT), has been identified as an additional candidate gene and displays high tissue expression in the brain [Collins and Cornish, 2002]. The dopaminergic system is involved in the pathophysiology of ADHD and DAT has been associated with the condition [Swanson et al., 2000], with mouse models that homozygously knockout DAT (DAT-KO) displaying severe hyperactivity [Giros et al., 1996; Spielewoy et al., 2000; Pogorelov et al., 2005]. Because the most severe phenotypes occur when both alleles are deleted, individuals that are hemizygous for *SLC6A3* may be uniquely sensitive to the detrimental effects of other ADHD-susceptibility alleles that have been reported for this gene [Tong et al., 2015].

DAT is the site of action of stimulant medications such as methylphenidate (MPH), which is used for treatment of ADHD [Volkow et al., 1998]. DAT-KO mice respond to MPH, while heterozygous mice initially respond but eventually develop sensitization. Alternate drugs such as fluoxetine or the dietary 5-HT precursor (*l*-tryptophan) targeting serotonergic

pathways also decreased symptoms in the DAT-KO mice [Spielewoy et al., 2001]. As 70% of children with 5p– are diagnosed with ADHD, characterization of their response or lack thereof to treatments such as MPH are needed. Future studies may explore whether alternate drugs may have improved efficacy for the treatment of ADHD in people with 5p– whose deletions include *SLC6A3*.

CDH18 (19,473,139–20,575,971), *CDH12* (21,750,869–22,853,730), *CDH10* (24,487,208–24,645,084), *CDH9* (26,880,708–27,038,688), *CDH6* (31,193,761–31,329,252): Cognition, ASDs

Multiple studies have suggested that cadherin genes may play a role in the 5p– cognitive phenotype. These genes encode for cell–cell adhesion molecules that play critical roles in brain development. All have demonstrated strong expression in the brain, with *CDH18, CDH10*, and *CDH9* playing a specific role in synapse formation and axonal growth [Barber et al., 2011; Williams et al., 2011; Oeschger et al., 2012]. However, deletions in these genes have also been observed in asymptomatic individuals, suggesting that the effects of cadherin hemizygosity may have incomplete penetrance. Barber et al. [2011] suggested that penetrance may be affected by the deletion of other flanking gene(s) and/or gene(s) associated with intellectual disability. Other modifiers of gene expression include modulation by microRNAs (miRNAs) and epigenetic factors.

CDH10, CDH9, and *CDH6* are reported to contribute to the genetic risk burden for susceptibility to ASDs [Wang et al., 2009; Jonsson et al., 2014]. GWAS studies show varying results as to whether single nucleotide polymorphisms in *CDH9* and *CDH10* have been associated with ASDs [Jonsson et al., 2014]. Whole exome sequencing also identified an association between *CDH6* and ASDs [Butler et al., 2015]. The mechanism by which variants in these genes contribute to ASDs is not defined; however, their role in the 5p– phenotype would be validated should there be a resulting dominant negative effect. Further studies of individuals with 5p– are needed to determine how allelic variation on the available copy affects phenotype when in combination with a deleted copy.

FUTURE DIRECTIONS

A primary goal of studying the natural history and molecular basis of 5p– is to develop a targeted therapy that will ameliorate or reverse its pathological features. When designing such a strategy for any genetic condition, there are many details to consider. After identifying a gene of interest, one must take into account practical considerations, that is, how and when to deliver the therapeutic, as well as examine its molecular and cellular properties. These properties include details such as when and where a gene is expressed, the molecular mechanisms required for normal expression, and the location and function of the final gene product. The timing of gene expression will determine the developmental or ontogenetic stage during which the therapeutic agent should be delivered in order to provide maximum benefits to the person.

Other factors include whether treatment is expected to be lifelong, or can be limited to a critical developmental period. Given that features of 5p– have been identified as early as the prenatal period in some individuals via abnormal maternal serum screening results and/or

ultrasound anomalies [Fankhauser et al., 1998; Weiss et al., 2003; Torun et al., 2009; Nguyen et al., 2014] and that candidate genes such as *CTNND2* are known to be active during fetal development [Matter et al., 2009], treatment during pregnancy may be considered in order to properly prevent the aforementioned features.

The location of normal gene expression will determine what specific tissues need to be targeted by the therapeutic. 5p– genes of interest such as *CTNND2, SLC6A3, CDH18, CDH12, CDH10*, and *CDH6* are known to be expressed in the brain [Medina et al., 2000; Collins and Cornish, 2002; Barber et al., 2011; Oeschger et al., 2012]. Therefore, a therapeutic agent must be able to cross the blood–brain barrier to be effective. It has been speculated that the blood–brain barrier is "leaky" in fetuses, which may facilitate drug delivery if treatment during embryonic development is found to be necessary [Saunders et al., 2012]. However, limitations include any untoward effects that may not be predictable.

The molecular mechanisms involved in normal gene expression range from the constitutional mechanisms of transcription, standard post-transcriptional modifications, and translation, to other gene-specific requirements. Gene-specific requirements may include processes such as alternative splicing, modulation by upstream or downstream silencers and enhancers, and mRNA regulation by molecules such as miRNAs. Other post-transcriptional or post-translational modifications may serve to target the final gene product to certain locations intracellularly or extracellularly Each of these mechanisms may provide a potential target for intervention. The location where these processes occur and that of the final gene product must also be taken into account when designing the therapeutic agent. Proteins may be present in multiple isoforms or function as part of a multi-subunit complex, which may provide further targets as well as challenges for researchers.

In order for a therapeutic agent to provide medical benefits, it must be targeted for delivery to the correct cellular location in appropriate tissues. Mode of delivery will determine what metabolic processes the agent will encounter before arriving to the cells. Agents delivered orally must avoid metabolic breakdown in the gut, and all modes that involve eventual delivery into the bloodstream will encounter metabolism in the liver. As mentioned previously, these agents will likely also be required to cross the blood–brain barrier to be effective in 5p–. When calculating the dosage needed in order to provide a therapeutic benefit, both the safety and efficacy of the therapeutic drug (or other agent) must be considered. In addition, agents that are taken orally may be more appealing to patients as compared to injection or infusion-based therapies.

Understanding how the deletion of a gene in an autosomal locus affects phenotype is essential to understanding the pathophysiology of the gene and will ultimately lead to the development of therapeutic technologies. Several therapeutic mechanisms have been explored in other genetic conditions with decreased protein activity or haploinsufficiency as the major pathological feature. These potential therapies may also have applications for treatment of 5p–, including protein or enzyme replacement therapy, pharmacological chaperones, protein transduction methods, gene therapy, histone deacetylase inhibitors, downregulation of inhibitory miRNAs, and transcriptional activation by zinc-finger proteins (ZFPs), clustered regularly interspaced short palindromic repeats-CRISPR-associated 9

system (CRISPR-Cas9), or transcription activator-like effector nucleases (TALENs). Some of these therapies have successfully become commercially available for patients, while others are in various stages of research and development. All potential avenues are specific to the pathogenic mechanism in the disease gene of interest, so further studies to identify and expand our knowledge of the critical disease genes and their molecular mechanisms is the first step in developing a targeted treatment for 5p–.

Protein or Enzyme Replacement Therapy

Protein or enzyme replacement therapy (ERT) is a useful strategy when the major pathological feature is the loss of an enzyme or protein. The missing product is delivered back to the appropriate cells, so that they are able to resume their normal function. This has been well studied with commercially available treatments in the context of recessive metabolic diseases [Schiffmann et al., 2001; Weinreb et al., 2002; Winkel et al., 2004; Wraith et al., 2004; Muenzer et al., 2006]. Truly personalized medicine would allow targeted treatment for subsets of people with 5p– in whom protein or enzyme activity is affected due to an autosomal recessive mutation in combination with their deletion, as discussed above. However, ERT is most efficient for delivering unmodified recombinant proteins to the lysosomal compartment, which may limit its utility for the treatment of 5p–. Therefore, ERT of modified (conjugated) proteins and the use of protein transduction technology [Ford et al., 2001], which are able to overcome this limitation, may bear greater promise for the treatment of 5p–.

Protein Transduction

Protein transduction allows for the delivery of therapeutic proteins across the blood–brain barrier and has been successful in delivery of proteins to diverse cellular compartments, such as the cytosol, lysosome, nucleus, and mitochondria [Schwarze et al., 1999, 2000]. As of 2011, there have been more than 20 phase I and II clinical trials employing drug delivery through protein transduction [Van Den Berg and Dowdy, 2011]. Other considerations for ERT and protein transduction methods include the additional amount of protein or enzyme activity required to achieve therapeutic benefit.

Pharmacological Chaperones

Pharmacological chaperones bind to and stabilize specific protein(s) to enable their proper folding and trafficking. Likewise, proteostasis regulators increase the proteostasis network capacity in a general way to restore proper proteostasis in the cell [Wang et al., 2014]. These strategies aim to overcome the effects of haploinsufficiency by improving the stability of wild-type proteins, and may be used in conjunction with other therapies such as ERT. For example, Benjamin et al. [2012] reported on the co-administration of the AT1001 pharmacological chaperone together with wild-type recombinant human a-galactosidase A (rha-Gal A), the current ERT for Fabry disease. The circulating half-life of rha-Gal A was increased by >2.5-fold in rat models. Gla KO mice displayed fivefold higher rha-Gal A levels and fourfold greater reduction of the pathological substrate GL-3 than when they received rha-Gal A alone. Similarly, increasing half-lives, and therefore steady-state levels, of intracellular 5p– associated proteins with pharmacological chaperones may have

therapeutic effects. Proteostasis regulators may also increase intracellular levels of 5p – proteins by reducing their degradation.

Gene Therapy

Therapeutic delivery of the wild-type gene, commonly known as gene therapy, may be limited for use in the treatment of 5p– conditions because of the need to induce precise gene dosage in order to achieve a clinically significant effect. In this therapy, an additional copy (or copies) of the wild-type gene are delivered to target cells using viral vectors. This strategy can be problematic in complex genes, such as those with multiple splice variants, in which case delivery of a large intron-containing segment of chromosomal DNA may be required. Positional effects must also be considered, such as possible consequences of regulatory elements in chromatin surrounding gene insertion site(s).

Gene therapy has traditionally been very limited in the mode and location of treatment delivery, both of which affect the yield of successful gene insertion and/or expression. However, proof-of-concept models in spinal muscular atrophy (SMA) and amyotrophic lateral sclerosis have been successful with a variation of gene therapy using novel serotypes of adeno-associated virus (AAV), such as AAV-9, which are able to infect numerous cell types and appear to cross the blood–brain barrier [Valori et al., 2010; Dominguez et al., 2011]. These models have been used to deliver transgenes in the form of episomes to adult motor neurons in mouse and cat models after intravenous delivery of the vector [Duque et al., 2009]. However, this approach is limited by the eventual loss of the episome and therapeutic gene following subsequent cell divisions. Despite their limitations, gene therapy trials have reported some remarkable successes, such as transfusion-independence of a beta-thalassemia patient 7 years after receiving gene therapy [Finotti et al., 2015]. As such, the first gene therapy drug has been recently approved by European regulators and will become clinically available this year [Morrison, 2015].

Histone Deacetylase Inhibitors

Another potential strategy may take advantage of epigenetic modification via histone deacetylase inhibitors [Echaniz-Laguna et al., 2008; Monani and De Vivo, 2014]. In general, histone acetylation, which is regulated by histone acetylases and histone deacetylases (HDACs), causes chromatin to be remodeled from a tightly packed configuration to a loosely packed configuration, thus augmenting transcriptional activation of local genes. HDAC inhibitors are a class of compounds that have been shown to increase gene expression through the suppression of HDAC activity [Kazantsev and Thompson, 2008]. Several of these compounds have been shown to increase SMN protein concentration via the *SMN2* gene in both cultured cells and animal models of SMA [Sumner et al., 2003; Grzeschik et al., 2005; Tsai et al., 2008; Riessland et al., 2010]. However, clinical trials have shown a modest effect at best in patients with SMA [Mercuri et al., 2004, 2007; Pane et al., 2008; Swoboda et al., 2009]. HDAC inhibitors are rather non-specific and, therefore, may increase the expression of multiple hemizygous genes in 5p–. However, expression of other genes throughout the genome may also be increased and cause unforeseen side effects. In concept, it seems possible that HDACs could be used to ameliorate the effects of

haploinsufficiency of 5p– genes if the limitations associated with the drugs' effectiveness in human patients can be overcome.

miRNA Inhibition

Modulation of post-transcriptional regulation mechanisms includes several potential therapeutic targets. Post-transcriptional modification of mRNA includes 5'-end processing and capping, 3'-end processing and polyadenylation, and splicing. These universal processes play a large role in regulating the stability of all mRNAs. A variety of cellular molecules, including endogenous miRNAs, are involved to perform these functions. Inhibition of specific miRNAs with the goal of increasing gene expression is currently being studied as a potential therapy to upregulate *ELN* expression in people with Williams–Beuren syndrome (WBS), caused by deletions on 7q. In WBS, deletion of the *ELN* gene results in less than 50% of normal gene expression when compared to wild-type, which suggests a role of post-transcriptional regulation of *ELN* mRNA levels. Supported by further mouse studies, this mRNA modification is hypothesized to play a large role in regulating *ELN* mRNA and protein levels in adults via a specific miRNA, miR-29a, which functions to downregulate the expression of *ELN, COL1A1*, and *COL3A1*. Inhibition of miR-29a has been shown to increase *ELN* expression in human cells from people with *ELN* haploinsufficiency and in bioengineered human blood vessels [Zhang et al., 2012a]. A specific miRNA has also been implicated in the negative regulation of the expression of *TBX1*, a key candidate gene for 22q11.2 deletion syndrome [Gao et al., 2015]. However, further studies are needed to determine if inhibition of this miRNA will have similar results to those shown for WBS. Similar strategies may also be studied in models of 5p– if critical genes are affected by decreased mRNA stability and/or targeted by specific miRNAs.

Transcriptional Activation

Transcriptional activation by ZFPs is another strategy being studied in the context of *ELN* expression in WBS. In this therapy, the remaining wild-type allele is upregulated in order to achieve sufficient gene expression. Targeting the wild-type allele also allows all other molecular mechanisms, such as alternative splicing, post-transcriptional modifications, etc., to remain in place and function normally. When engineered ZFPs were used to induce augmented expression of the wild-type *ELN* allele in WBS cell culture models, the expressed ELN protein was present in its major splice variants and in its natural stoichiometry. In addition, ZFP-induced *ELN* expression in bioengineered blood vessels was shown to be capable of functional elastogenesis [Zhang et al., 2012b]. Recently, transcriptional activation with CRISPR-Cas9 [Konermann et al., 2015] and TAL effectors [Zhang et al., 2011] emerged as an efficient alternative to ZFPs. By altering the design of TAL effectors and CRISPR-Cas9, one can regulate induction of endogenous genes in the 2- to 50-fold range [Zhang et al., 2011; Tanenbaum et al., 2014] and thus modulate therapeutic efficiency. These methods may provide additional strategies to target upregulation of specific 5p– genes of interest.

DISCUSSION

Continued natural history studies with precise genotyping are imperative to further define the genes associated with the features of individuals with 5p–, as well as inform us of the health needs of adults with this condition. Several medical and behavioral studies using relatively large cohorts have been conducted [Wilkins et al., 1983; Cornish and Pigram, 1996; Dykens and Clarke, 1997; Mainardi et al., 2001; Collins and Cornish, 2002]. However, natural history studies of 5p– such as those from Posmyk et al. [2005] and Mainardi [2006] are rare, despite the fact that many children are diagnosed within the first year of life [Mainardi, 2006]. One limitation of this review is that the 5p Minus Family Database does not have high resolution copy number data to correlate with each individual. Subsequent natural history studies focused on the specific hemizygous genes and their associated phenotypes will be essential for delineating the consequences of 5p deletions, subsequently allowing the clinician to provide more targeted risk assessments for specific phenotypic features based on the genes included in an individual's deletion. These studies stand in contrast to traditional descriptive studies that combine all individuals with 5p – and determine the frequencies of various features.

There are many barriers for the completion of longitudinal studies [Doyle and Golding, 2009]. Nevertheless, natural history studies are central for the development of therapeutic agents [Workshop on Natural History Studies of Rare Diseases, 2012]. The functions of most genes on 5p are still unknown. Genotype–phenotype studies of large cohorts of individuals with 5p– may define critical regions that are associated with the condition [Church et al., 1997; Mainardi et al., 2001; Kondoh et al., 2005; Wu et al., 2005; Zhang et al., 2005; Wang et al., 2009; Krgovic et al., 2014]. People with other chromosomal anomalies involving breakpoints in the 5p– critical regions may provide additional insight into gene function by careful observation of their phenotype. Specific attention should be given to these types of people when they are identified in the future, for they may uniquely assist in delineating genotype– phenotype correlations.

There are many barriers for the completion of longitudinal studies. Nevertheless, natural history studies are central for the development of therapeutic agents.

As new molecular testing technologies such as chromosomal microarrays and RNA sequencing (RNAseq) are refined, clinicians benefit from increased resolution and specificity when identifying what genes are affected by a given chromosomal deletion. These technologies, along with the decreasing costs and increasing uptake of testing, will allow a greater number of people to be identified with 5p–, including individuals who may not display the classic phenotype as it was initially described. Historically, most people with 5p– have been diagnosed through fluorescence in situ hybridization or karyotype [Mainardi, 2006]. Utilizing chromosomal microarray and RNAseq analyses could determine more specific breakpoints for deletions and lead to better genotype–phenotype correlations. These methods also have the ability to reveal additional duplications or deletions unidentified by former diagnostic methods [Miller et al., 2010] that might play a role in the individual's phenotype. Ultimately, the utilization of multiple technologies will be needed to help determine the roles of various genes.

The uptake of noninvasive prenatal screening and prenatal chromosomal microarray analysis, both of which can detect microdeletions [Wapner et al., 2015], will lead to an earlier diagnosis of 5p– than previously experienced. This shift will also reverse the traditional diagnostic approach, whereby individuals receive a diagnosis based on phenotype that is then confirmed by molecular testing; now, initial diagnosis of individuals will be first based on their molecular genotype, followed then by close monitoring of their emerging phenotype. Earlier diagnosis provides the opportunity to glean more natural history information from neonates and children, to closely monitor their onset of symptoms, and thus may further widen the known phenotypic spectrum of 5p–. Ultimately, early identification allows the opportunity for early treatment of 5p– disorders.

CONCLUSION

5p– has a well-described characteristic phenotype; however, the clinical spectrum is evolving. Progress toward developing a targeted therapy for 5p– is dependent on understanding the contribution of specific genes to the clinical manifestations of 5p–. This goal can be achieved through further phenotypic characterization of the condition in conjunction with genotypic characterization and in vivo models. This review demonstrates the tremendous amount of work that has been done thus far to better understand individuals affected with 5p–; however, it also highlights the need for additional studies aimed toward the goal of translation for improved patient care and outcomes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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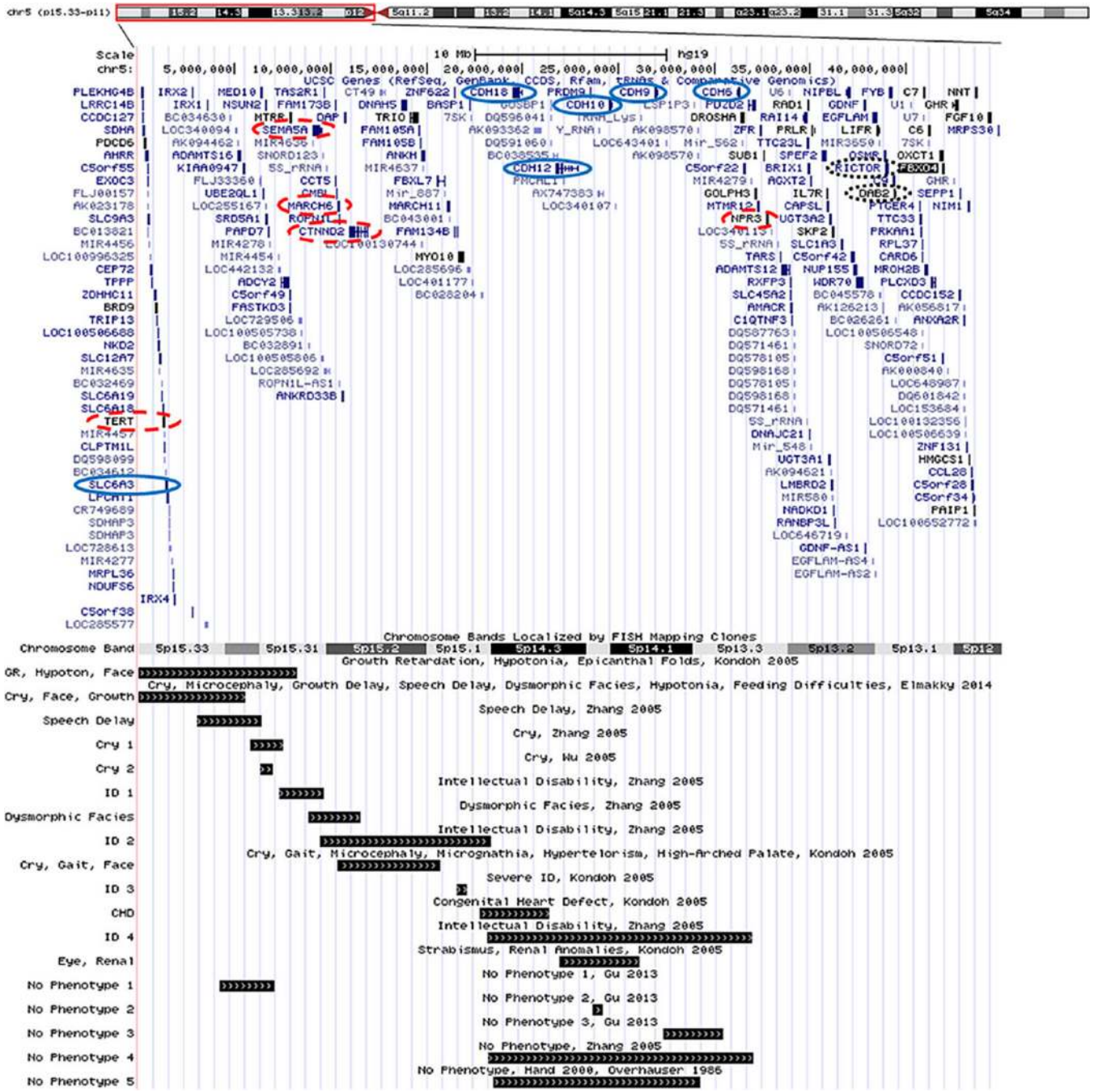

Figure 1.

Chromosome 5p gene dosage map. The red box around the chromosome 5 ideogram at the top indicates the region highlighted below. The abbreviations for the genes are listed to the left. Genes that demonstrate dosage effects are circled. Red circles with dashed lines indicate that the mechanism of disease is haploinsufficiency, blue circles indicate that the gene is a risk factor for disease (conditionally haploinsufficient), and black circles with dotted lines indicate hemizygous lethality (haplolethal). Corresponding chromosome bands and critical

regions for specific phenotypic features are also aligned. Adapted from the UCSC Genome Browser (04/2015).

Figure 2.
Left to right: Christina (21 years old), Brielle (9 years old), and Jack (22 months old) with 5p deletions. Photos by Rick Guidotti of Positive Exposure.

TABLE I

Genes on Chromosome 5p That Have Haploinsufficient and Conditionally Haploinsufficient Effects

Locus	Cytogenetic location	Gene symbol	Gene name	OMIM
Haploinsufficient				
1,253,281–1,295,177	5p15.33	*TERT*	Telomerase reverse transcriptase	187270
9,035,137–9,546,232	5p15.31	*SEMA5A*	Semaphorin 5A	609297
10,353,750–10,440,499	5p15.2	*MARCH6*	Membrane-associated Ring-Ch finger protein	613297
10,971,951–11,904,154	5p15.2	*CTNND2*	Catenin, delta-2	604275
32,710,283–32,791,829	5p13.3	*NPR3*	Natriuretic peptide receptor C	108962
Conditionally haploinsufficient				
1,392,790–1,445,428	5p15.33	*SLC6A3*	Solute carrier family 6 (neurotransmitter transporter, dopamine), member 3	126455
19,473,139–20,575,971	5p14.3	*CDH18*	Cadherin 18	603019
21,750,869–22,853,730	5p14.3	*CDH12*	Cadherin 12	600562
24,487,208–24,645,084	5p14.2–p14.1	*CDH10*	Cadherin 10	604555
26,880,708–27,038,688	5p14.1	*CDH9*	Cadherin 9	609974
31,193,761–31,329,252	5p13.3	*CDH6*	Cadherin 6	603007