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ARTICLE

A Review of 18p Deletions

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Since 18p- was first described in 1963, much progress has been made in our understanding of this classic deletion condition. We have been able to establish a fairly complete picture of the phenotype when the deletion breakpoint occurs at the centromere, and we are working to establish the phenotypic effects when each gene on 18p is hemizygous. Our aim is to provide genotype-specific anticipatory guidance and recommendations to

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families with an 18p- diagnosis. In addition, establishing the molecular underpinnings of the condition will potentially suggest targets for molecular treatments. Thus, the next step is to establish the precise effects of specific gene deletions. As we look forward to deepening our understanding of 18p-, our focus will continue to be on the establishment of robust genotype–phenotype correlations and the penetrance of these phenotypes. We will continue to follow our 18p- cohort closely as they age to determine the presence or absence of some of these diagnoses, including spinocerebellar ataxia (SCA), facioscapulohumeral muscular dystrophy (FSHD), and dystonia. We will also continue to refine the critical regions for other phenotypes as we enroll additional (hopefully informative) participants into the research study and as the mechanisms of the genes in these regions are elucidated. Mouse models will also be developed to further our understanding of the effects of hemizygosity as well as to serve as models for treatment development.

KEY WORDS: 18p deletion; 18p-; monosomy 18p

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INTRODUCTION

18p- was first described in 1963 by de Grouchy and colleagues. The main features as reported in the early reports include cognitive impairment, small stature, minor facial dysmorphism, ptosis, and strabismus [de Grouchy, 1969]. Holoprosencephaly and its microforms were also frequently reported. As the number of case reports increased, additional findings were described, to include speech and language difficulties, pituitary abnormalities, and, in some cases, IgA deficiency [Schinzel et al., 1974; Artman et al., 1992; Gul et al., 1994; Schober et al., 1995; McGoey et al., 2011]. More recently, the phenotype has expanded to include dystonia and autoimmune conditions, such as rheumatoid arthritis [Finley et al., 1972; Gluckman, 1977; Jones, 1982; Brown et al., 2003; Graziadio et al., 2009; Postma et al., 2009; Recalcati et al., 2010; Kowarik et al., 2011]. As is the case with many chromosomal abnormalities, however, the earliest reports had little information about breakpoints or genotype–phenotype correlations. In addition, data on long-term outcome as well as behavioral challenges are sparse. In the day and age of microarray technology and new tools to assess cognition and behavior, it is certainly time to update our knowledge of this "classic" chromosome deletion. With this in mind, the Chromosome 18 Clinical Research Center has been working to clarify and expand our knowledge of 18p- from both a clinical and molecular standpoint. We hope to be able to provide genotype-specific anticipatory guidance and recommendations, and, ultimately, to develop treatments for 18p-.

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MOLECULAR CHARACTERIZATION

Unlike its counterpart on the long arm of chromosome 18, deletions of 18p have some degree of genetic homogeneity. Approximately half of cases have breakpoints in the centromeric region [Schaub et al., 2002]. The remainder of the breakpoints are scattered along the entirety of the short arm. Interestingly, there have been no reports of large interstitial deletions of 18p, though there have been some microdeletions reported [Myers et al., 2014]. Approximately half of the deletions, regardless of breakpoint location, occur on the maternal chromosome [Schaub et al., 2002]. Since our initial reports over a decade ago, we have continued to genotype all study enrollees, now using microarray technology as described in Heard et al. [2009]. Our cohort currently includes 106 individuals with 18p-. Of these, 98 have had microarray completed. Within our cohort, 41 people (42%) had breakpoints within the centromeric region. The remaining breakpoints are scattered along the rest of the p arm of the chromosome (Fig. 1).

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Ninety-one had either an isolated deletion of 18p or an unbalanced translocation involving 18 and an acrocentric chromosome. The remaining participants had 18p- in addition to another chromosome imbalance. The large majority (89%) of our study participants had de novo isolated deletions. This is

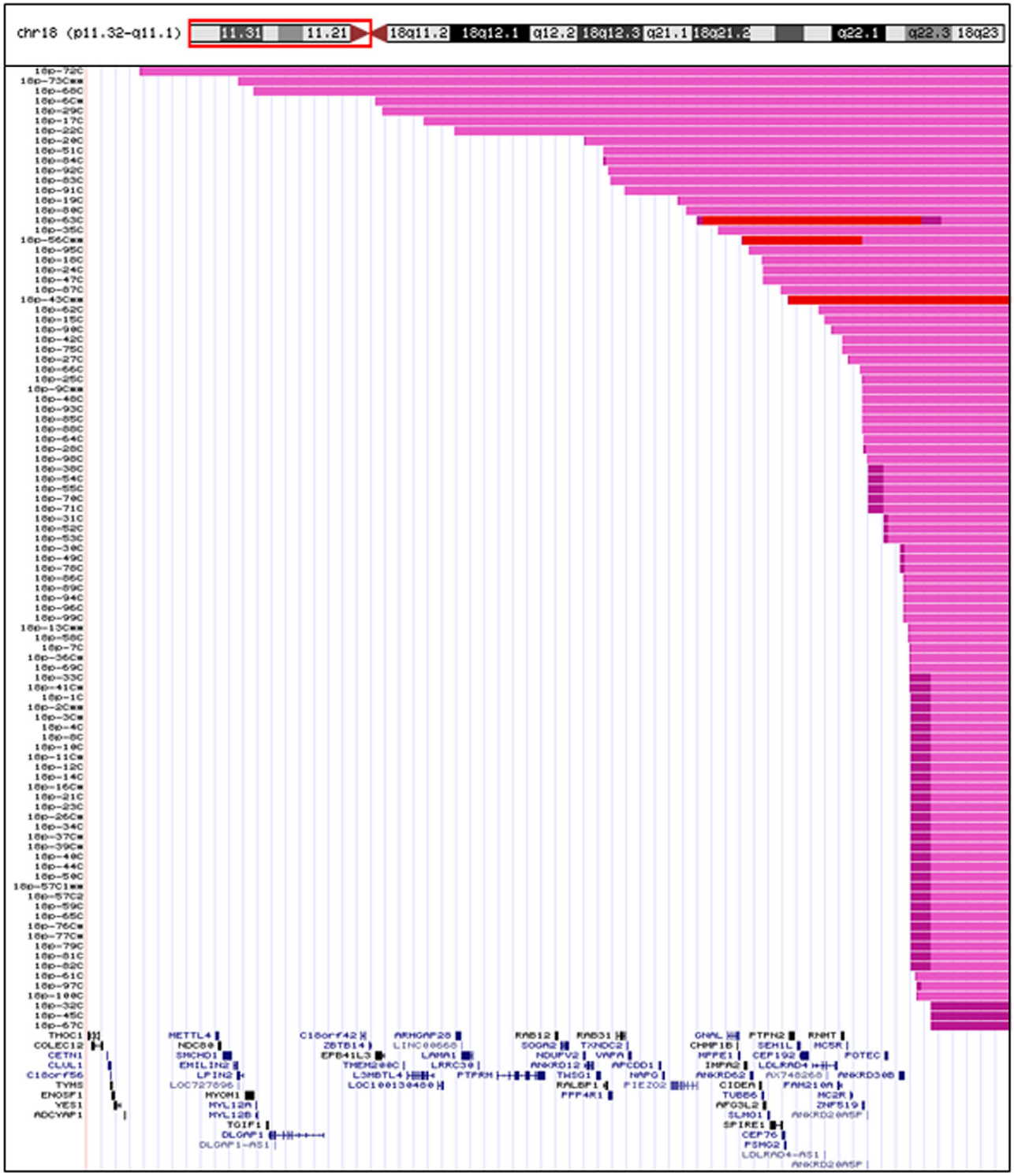

Figure 1. Chromosome 18 content for individuals with 18p hemizygosity. The red box around a portion of the chromosome 18 ideogram at the top indicates the region highlighted below. Each individuals' intact chromosome is indicated by the light gray (pink) bar with the individuals study number written to the left. The dark gray (dark pink) line at the end of each bar depicts the breakpoint region. The gaps in the bar indicate the map location of the homozygous region. The genes on 18p are shown below.

slightly different from the figures frequently cited in the literature. Schinzel et al. [2001] reported that 2/3 of cases are due to de novo deletions.

While 18p- is typically a de novo occurrence, there are reports of direct parent-to-child transmission of the deletion. Within our cohort, there is one case of a transmission from a parent to a child. Multiple cases of parental transmission have also been reported in the literature [Uchida et al., 1995; Velagaleti et al., 1996; Tonk and Krishna, 1997; Rigola et al., 2001; Tsukahara et al., 2001]. In all of these reports, the deletion was inherited from the mother.

In 56 of the de novo cases, parental origin of the deletion was able to be determined. In 25 of the cases, the deletion occurred on the paternal chromosome. In the remaining cases, the deletion occurred on the maternal chromosome. This is consistent with what has been reported in our center as well as in other manuscripts [Schaub et al., 2002; Wester et al., 2006].

CLINICAL PRESENTATION OF CENTROMERIC 18P-

The largest challenges in the description of a chromosome abnormality are the variability of the breakpoints as well as variable penetrance. As discussed above, however, 18p- has some degree of genetic homogeneity, as nearly 50% of individuals with 18p- have a breakpoint in the centromeric region (Fig. 1). This provides a baseline for a "typical" 18p- presentation, in which at least the breakpoint is consistent. This phenotype has recently been reported in Sebold et al. [2015]. The primary clinical features of centromeric 18p- are listed in Table I. Images of individuals with centromeric as well as non-centromeric breakpoints are included in Figures 2 and 3.

Other conditions have also been linked with 18p- but were not present in our centromeric population, such as dystonia [Klein et al., 1999; Graziadio et al., 2009; Postma et al., 2009; Kowarik et al., 2011]. Ulerythema ophryogenes in conjunction with keratosis pilaris has been reported in individuals with 18p- [Zouboulis et al., 1994, 2001; Nazarenko et al., 1999; Carvalho et al., 2011; Liakou et al., 2014].

Data regarding the developmental and behavioral phenotypes of centromeric 18p- have been reported as well. It has been well-documented that developmental delays and cognitive impairment are common in individuals with 18p- [Weiss et al., 1969; Parker et al., 1973; Turleau, 2008]. More recently, the extent of cognitive impairment in children and young adults was reported. In Sebold et al., the average full scale IQ was 69 and ranged from 51 to 99 [2015]. Thus, the extent of cognitive impairment typically falls into the mild to borderline range.

In Sebold et al., the average full scale IQ was 69 and ranged from 51 to 99.

In addition to data regarding cognitive ability, we have also reported on the behavioral phenotype of individuals with centromeric 18p-. The majority of participants have problems with activities of everyday life, which includes difficulties with communication, home living, self-care, and management of social and leisure activities [Sebold et al., 2015]. It also appears that the centromeric 18p- population is at a slightly increased risk for autism, based on parental report. Based on the GARS (Gilliam Autism Rating Scale) survey, four of 21 were rated as being very likely to have autism and four that were rated as possibly having autism, suggesting that the prevalence of autism in those with whole p arm deletions is likely to be between 19 and 38%.

GENE DOSAGE MAP

As discussed above, our understanding of the clinical features of 18p- is fairly substantial for those with whole p arm deletions. This serves as a baseline for our journey towards full understanding and treatment of this condition. The next steps towards a full understanding of this condition will be the identification and characterization of each dosage sensitive gene on 18p. This information will allow for more precise and personalized anticipatory guidance based on an individual's specific breakpoints. In addition, it will provide targets for molecular treatments.

There are two strategies to establish these correlations:

(1) Verify the role of putative dosage sensitive genes by reverse phenotyping, that is, taking genes of interest and determining the relevant phenotype, if any, in those individuals with deletions inclusive of that gene.
(2) Genotype–phenotype correlations to identify critical regions, and, eventually, candidate genes.

Dosage Sensitive Genes

We are using reverse phenotyping to uncover the effects of the deletions of specific genes. In essence, we are looking at genes on 18p that are thought to be dosage sensitive to determine the clinical outcome in individuals with 18p-. In recent years, several genes on 18p have been identified as possibly being dosage sensitive. Of the 67 genes on 18p, twelve are thought to either lead to haploinsufficiency or are conditionally dosage sensitive.

CETN1 (580,369-581,524)

As with other centrins, this gene plays a role in the determination of centrosome position and segregation as well as in the appropriate actions of microtubules. Mouse models carrying heterozygous mutations in the gene are infertile [Avasthi et al., 2013]. There have been no reports of a direct transmission of a deletion from a father to a child. There have, however, been multiple mother to child transmissions [Uchida et al., 1965; Velagaleti et al., 1996; Tonk and Krishna, 1997; Rigola et al., 2001; Tsukahara et al., 2001]. Based on the breakpoint discussed in these papers, the deletions would have included *CETN1,* suggesting that hemizygosity of this gene does not cause infertility in females. In our own cohort of 22 adult males, none have children [Soileau et al., 2014]. However, it is unknown whether any have attempted to start a family, and no

Figure 2. People with centromeric 18p deletions.

measures have been taken to determine fertility status.

TGIF1 (3,451,591-3,458,406)

TGIF is a homeodomain protein that plays a role in transcriptional regulation in the TGF signaling pathway. In 2000, point mutations in this gene were linked with holoprosencephaly [Gripp et al., 2000]. Indeed, holoprosencephaly and its microforms are well-known features of 18p-, occurring in as much as 10% of patients. More recently, the question about whether this gene may also be linked to other midline defects that are not considered to be "classic" holoprosencephaly, such as isolated pituitary stalk anomalies, has been raised [Tatsi et al., 2013]. Indeed, other authors have considered pituitary abnormalities as a microform of HPE [Rosenfeld et al., 2010].

Of note, there has been a suggestion that another gene on 18p plays a modifying role. One study suggested that deletions encompassing both *TWGS1* (located at 9,334,765-9,402,418) and *TGIF1* are associated with a higher penetrance of HPE and its microforms than if *TGIF1* alone is deleted [Rosenfeld

Figure 3. People with non-centromeric 18p deletions.

et al., 2010]. However, a follow up study suggested that *TWSG1* is actually unlikely to play a role in the HPE phenotype [Kauvar et al., 2011].

In our 18p- population hemizygous for *TGIF1*, 11% (6/65) had malformations on the holoprosencephaly (HPE) spectrum. One individual had HPE lobar type while several others had an HPE microform. Four had a single central incisor, and one presented with an iris coloboma. In addition to these six,

TABLE I. Features Associated With Centromeric18p- and Their Frequency

Finding	Frequency (%)
Hypotonia/mixed tone abnormalities	84
Neonatal complications (jaundice, respiratory distress, feeding difficulties)	71
MRI anomalies (excluding HPE spectrum)	66
Recurrent otitis media	61
Heart defects	56
Ptosis	55
Refractive errors	52
Strabismus	42
Pectus excavatum	29
Hearing loss	23
Isolated growth hormone deficiency	23
Scoliosis/kyphosis	19
Pes planus	19
Cryptorchidism	14
Panhypopituitarism or hypopituitarism	13
Seizures	13
IgA, IgG, or IgM deficiency	13
Holoprosencephaly or HPE microform	13
Autoimmune disorder	10
Sacral agenesis	6
Optic nerve hypoplasia	6
Congenital cataracts	6
Myelomeningocele	3

several others had structural pituitary abnormalities, including a hypoplastic pituitary; absent posterior pituitary gland; complete absence of the pituitary gland; and a hypoplastic pituitary stalk. All of these individuals had deletions that also encompassed *TWSG1*.

In our 18p- population hemizygous for TGIF1, 11% (6/65) had malformations on the holoprosencephaly (HPE) spectrum. One individual had HPE lobar type while several others had an HPE microform.

Additionally, there has been a report suggesting that the *TGIF1* knock-out mouse has a thickened middle ear mucosal lining leading to chronic otitis media and conductive hearing loss [Tateossian et al., 2013].

LAMA1 (6,941,743-7,117,813)

The *LAMA1* gene product, in conjunction with LAMB1 and LAMB2, forms a basement protein [Paulsson et al., 1985]. In mice, it appears to be expressed in the basal lamina of renal cortical tubules, testis seminiferous epithelium, and in the retina [Edwards et al., 2010]. Chemically induced mutations in *LAMA1* result in a retinal vasculopathy, characterized by vitreous fibroplasia and vessel tortuosity [Edwards, 2011]. No such findings have been described in humans in the literature, either with a point mutation or in the context of 18p-. There has also been a suggestion that hemizygosity of *LAMA1* may be linked to ulerythema ophryogenes, and keratosis pilaris [Zouboulis et al., 2001].

In the participants hemizygous for *LAMA1*, one of 32 had been diagnosed with tortuous anomalous vessels (3%). Keratosis pilaris was a common finding within the cohort, present in seven individuals. However, no one had been diagnosed with ulerythema ophyrogenes.

It is worth noting that anomalies of the retinal vasculature have also been reported in association with facioscapulohumeral muscular dystrophy (FSHD), which has been linked to a more distal gene on 18p (*SMCHD1*), discussed below [Matsuzaka, 1986; Bindoff, 2006].

Of interest, individuals with homozygous as well as compound heterozygous mutations within *LAMA1* have been diagnosed with Poretti-Bolshauser syndrome, which is characterized by cerebellar anomalies, high myopia, retinal dystrophy, and ocular abnormalities as well as developmental delays and cognitive impairment [Aldinger et al., 2014]. Although Poretti-Bolthauser syndrome is autosomal recessive, it is theoretically possible that rare individuals with 18p- may have features of this condition due to a revealed recessive mutation.

GNAL (11,689,014-11,885,683)

GNAL codes for a subunit of the G protein receptor. In 2013, Fuchs et al. reported the identification of several patients with dystonia with point mutations in *GNAL* [Fuchs et al., 2013; Vemula et al., 2013]. GNAL seems to be the most frequent and currently most documented cause of adult-onset segmental dystonia [Lohmann and Klein, 2013]. Dystonia has been reported in individuals with 18p-, and it is likely that this gene is responsible for this particular aspect of the conditions [Graziadio et al., 2009; Postma et al., 2009; Kowarik et al., 2011; Esposito et al., 2014].

Seventeen individuals with deletions inclusive of GNAL were evaluated by our neurologist (SA). None met the diagnostic criteria for dystonia [Comella et al., 2003]. Review of medical records showed that two (3%) of 58 individuals with deletions encompassing GNAL had dystonia. One individual was

diagnosed with torsion dystonia. Another individual was also diagnosed with torsion dystonia during early childhood. In addition, one individual hemizygous for *GNAL* was diagnosed with myoclonus events at age 13 years old, but no diagnosis of dystonia was made.

AFG3L2 (12,328,943-12,377,275)

This gene codes for a subunit of a mitochondrial protease that plays a role in the degradation of misfolded proteins as well as in ribosome assembly. The gene product is found in higher concentrations in post synaptic densities [Bayés et al., 2011]. Point mutations in this gene have been linked to spinocerebellar ataxia, type 28 [Di Bella et al., 2010]. SCA28 is characterized by a progressive ataxia with an onset in young adulthood. Other features may include speech difficulties (dysarthria), hyperreflexia, and ocular anomalies, to include nystagmus and ptosis [Brussino et al., 2011]. Isolated SCA28 is inherited in an autosomal dominant pattern.

Up to this point, the grand majority of disease-causing mutations have been located in a protease domain for the protein product. Recently, there has been one case report in which a microdeletion encompassing three genes (including *AFG3L2*) has been reported in an individual with multiple cytogenetic abnormalities [Myers, 2014]. This individual had a progressive ataxia with an onset at 13 years of age in addition to developmental delays, suggesting that full gene deletions can present with the same phenotype as point mutations. Deletions and duplications of this gene have been found in control populations, suggesting that penetrance is incomplete [MacDonald et al., 2013].

Fifteen individuals that are hemizygous for the *AFG3L2* gene underwent a physical exam by one of the authors. None met the diagnostic criteria necessary for diagnosis of SCA28 [Schmitz-Husbsch et al., 2006, 2010; Weyer et al., 2007]. In addition, no one in our cohort has been diagnosed with a cerebellar ataxia. However, the cohort is still relatively young. It may be that, as they age, some individuals are diagnosed with SCA28.

PTPN2 (12,792,301-12,884,334)

Several studies have linked mutations in this gene with inflammatory bowel disease, including mouse studies and GWAS studies [Hassan et al., 2010; Glas et al., 2012]. These findings have been confirmed by meta-analysis [Zhang et al., 2014]. Of note, ulcerative colitis and Crohn's disease are not recognized features of 18p-. However, there has also been a suggestion of a link between *PTPN2* and rheumatoid arthritis and type 1 diabetes [Todd et al., 2007; Okada et al., 2012]. Rheumatoid arthritis has been reported in individuals with 18p- [Finley et al., 1972; Czakó et al., 2002; Recalcati et al., 2010]. Thus, it seems plausible that *PTPN2* plays a role in etiology of autoimmune disease.

No one in our group of 67 individuals hemizygous for *PTPN2* has been diagnosed with inflammatory bowel disease (IBD). However, 11 of the 67 had an autoimmune condition, to include juvenile rheumatoid arthritis, Sjogrens syndrome, hypothyroidism, graves, celiac, vitiligo, psoriasis, and alopecia. One additional individual had rheumatoid arthritis but the deletion was not inclusive of *PTPN2*. In fact, this individual was used to define the critical region discussed below. It is, however, possible that this individual's deletion interferes with some regulatory regions that play a role in the expression of *PTPN2*.

There are six genes that we hypothesize cause conditional haploinsufficiency. Hemizygosity of these genes requires at least one additional event, such as another genetic variation or an environmental exposure, in order for an abnormal phenotype to develop. Consequently, these genes are frequently found to be deleted or duplicated in multiple control individuals [MacDonald et al., 2013]. Those genes are:

SMCHD1 (2,655,886-2,805,015)

The presence of a structural maintenance of chromosomes hinge domain suggests that the gene product of *SMCHD1* plays a role in X-inactivation as well as methylation [Blewitt et al., 2008]. In 2012, Lemmers et al. reported a link between point mutations in this gene and FSHD. FSHD typically presents during the teen years and is characterized by weakness of the facial muscles, scapular stabilizers, upper arms, lower legs, and hip girdle [Lemmers et al., 1999]. The condition is extremely variable and slowly progressive. FSHD is caused by expression of the normally repressed *DUX4* gene that lies within the D4Z4 repeat domain on chromosome 4q. The *SMCHD1* gene is responsible for the maintenance of this repression by heavily methylating the D4Z4 chromatin domain created by 10–100 of these repeats. FSHD1 occurs when this D4Z4 repeat is smaller than 10 repeats and occurs in conjunction with a "permissive allele," that is, a polyadenylation signal immediately distal to the *DUX4* retrogene. Together, this leads to chromatin relaxation and inappropriate expression of the *DUX4* gene. Individuals with FSHD2 have D4Z4 repeat numbers in the low normal range (11–16 repeats). However, they also carry mutations in or deletions of the *SMCHD1* gene. When this occurs in the context of a *DUX4* permissive allele, this leads to the relaxation and expression of *DUX4*, and subsequently the FSHD phenotype [Lemmers et al., 2012]. Lemmers et al. [2015] recently found that about one in eight individuals with 18p- have less than 16 repeats as well as the permissive allele, putting them at risk to develop FSHD.

One of the authors (SA) is a neurologist and performed physical exams on 21 individuals with deletions inclusive of *SMCHD1*. For each individual, the neurologist completed the "Physical and Functional Examination for Phenotypic Facioscapulohumeral Dystrophy (FSHD) Scale," which was developed by Rabi Tawil, MD, and based on the work of Ricci et al., [1999] and van Overveld et al. [2005]. None of these individuals were diagnosed with FSHD. In addition, 89 medical records were reviewed, and no one had been diagnosed with FSHD. It is possible that this is because our cohort is relatively young. Of the 21 people evaluated in person, the average age was 18 and ranged from 8 to 30 years of age.

Of interest, one individual with a deletion including this gene has been diagnosed with exudative retinopathy, an uncommon, but documented, feature of FSHD [Bindoff, 2006].

Interestingly, this gene was differentially expressed in the amniotic fluid of fetuses with trisomy 18 [Koide et al., 2011].

TWSG1 (9,334,765-9,402,418)

Xenopus and zebrafish homologs of this gene appear to play a role in dorsal-ventral patterning during embryologic development [Oelgeschläger et al., 2000; Ross et al., 2001]. In addition, studies in mice have suggested it is involved in craniofacial development [Petryk et al., 2004]. Lastly, heterozygous knockout mice that have been exposed prenatally to retinoic acid are at a significant risk for facial deformities (30%), holoprosencephaly (23%), and neural tube defects (7%) [Billington et al., 2015].

In humans, as discussed above, it has been suggested that this gene interacts with *TGIF1* and plays a role in holoprosencephaly phenotype. However, another study has called this finding into question. There are no individuals within our study cohort with HPE that are hemizygous only for *TWSG1*; however, there is one individual with a deletion breakpoint between the two genes (hemizygous for *TGIF1* and homozygous for *TWSG1)* that had Goldenhar syndrome. Additional research will be necessary to determine the effect of deletions of this gene and whether it interacts with *TGIF1.*

In addition, a GWAS study showed a suggestive association between *TWSG1* and dental caries, a less common phenotype in people with 18p deletions [Hermesch et al., 2000; Shaffer et al., 2013].

Candidate Genes for Autism

As discussed above, there is some evidence that individuals with 18p- are at a somewhat increased risk for autism [Sebold et al., 2015]. There have been several genes on 18p identified as potentially playing a role in the etiology of autism spectrum disorders. *DLGAP1* (3,499,183-3,880,068) has been proposed because the gene product is enriched in post synaptic densities, implying a role in autism [Betancur et al., 2009; Bayés et al., 2011]. In addition, a recent study has implicated three additional 18p genes: *LCCR30* (7,231,137-7,232,042), *ANKRD12* (9,136,751-9,285,983), and *IMPA2* (11,981,427-12,030,885) [Pinto et al., 2010]. Within our entire 18p-cohort, 56 families have completed the GARS or GARS-2 survey, which assesses the probability of a diagnosis of an autism spectrum disorder [Gilliam, 1995, 2006]. Of these, eight had scores in the "clinically significant" range, suggesting a diagnosis of autism. Seven of eight had deletions of *DLGAP1*, *LCCR30*, *ANKRD12*, and *IMPA2*. One individual was hemizygous for *DLGAP1*, *ANKRD12*, and *LRRC30* but homozygous for *IMPA2*.

CRITICAL REGIONS

There are several phenotypes associated with 18p deletions for which the causative dosage sensitive gene has not been identified. However, we are able to identify a critical region of the chromosome within which the causative genes are hypothesized to be located. Some critical regions have been suggested in the past, though they are rather large regions and have not been refined since their initial identification [Wester et al., 2006; Brenk et al., 2007].

Using the methodology described in Cody et al. [2009], the critical regions as well as the penetrance for each of the following phenotypes was determined: sensorineural hearing loss; strabismus; conductive hearing loss; ptosis; scoliosis/kyphosis; nystagmus; white matter abnormalities; cryptorchidism; kidney abnormalities; sacral agenesis; pectus excavatum; tetralogy of Fallot, structural pituitary anomalies; seizures; autoimmune conditions; congenital cataracts; and congenital hip dysplasia (Fig. 4, Tables II, and Supplementary Table S1). There are no interstitial deletions of 18p in our cohort, thus all of the critical regions extend from the telomere to the breakpoint of the individual with the smallest deletion. In addition, detailed descriptions of each of the phenotypes listed are included below.

Sensorineural Hearing Loss

Seven individuals had SNHL, two of whom had conductive hearing loss as well. Most of them had minimal to moderate hearing loss.

Conductive Hearing Loss

Fifteen individuals had bilateral conductive hearing loss and three had unilateral CHL. The degree of CHL was typically in minimal to mild range. The region for conductive hearing loss excludes *TGIF1*, which has been suggested to play a role in chronic otitis media and the resulting conductive hearing loss. It is possible that there is a second locus on 18p that plays a role in the phenotype.

Pituitary Anomalies

Of the 54 individuals that have had MRI's, six had some kind of pituitary abnormality. These anomalies included hypoplastic pituitary; absent posterior pituitary gland; complete absence of the pituitary gland; and a hypoplastic pituitary stalk.

Of note, another five individuals had hypothyroidism but no indication of a structural pituitary abnormality on MRI.

White Matter Abnormalities

Of the 54 individuals that have had MRI's, 26 had white matter abnormalities. An additional two had unclear reports, and it could not be determined whether white matter anomalies were present. In the 26 that had anomalies, several different types were noted, including delayed myelination; subtle thinning of white matter; white matter signal abnormalities; white matter changes due to ischemic insult; and T2 hyperintensities.

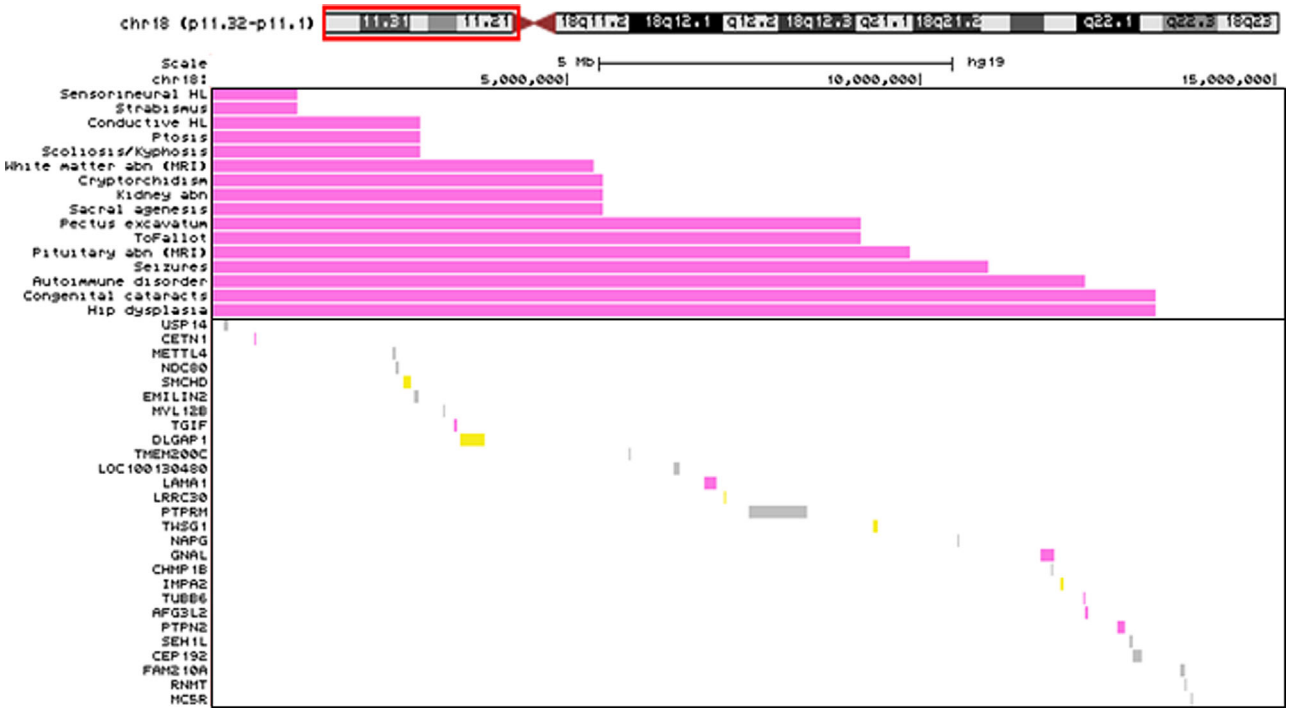

Figure 4. The Chromosome 18p Gene Dosage Map. The red box around a portion of the chromosome 18 ideogram at the top indicates the region highlighted below. The lower panel shows the chromosome regions associated with phenotypes and the genes in the region. The abbreviations for the regions and genes are listed to the left. Both are color coded by the molecular mechanism of disease as it relates to gene dosage. Pink (dark gray) indicates that the mechanism of disease is haploinsufficiency, yellow (light gray) indicates that the gene is a risk factor for disease and gray means the mechanism of disease is unknown. Not included in this figure are those regions and genes not associated with gene dosage abnormalities. However, all the regions and genes in all dosage classifications can be viewed at (http://pediatrics.uthscsa.edu/centers/Chromosome18/dosage.asp) The data on this website are also continuously updated as new information on gene function is learned.

Autoimmune Disorders

Three individuals had rheumatoid arthritis, one of whom also had Celiac disease and alopecia universalis. Several additional autoimmune conditions were reported, to include celiac disease (2); alopecia (2); psoriasis (1); Sjogrens (1); lupus (1); vitiligo (2) (one of whom also had alopecia). Five had autoimmune hypothyroidism manifested as: Graves' disease (1), multinodular goiter (1), and hypothyroidism (3).

It is interesting to note that the critical region for autoimmune disorders does *not* include *PTPN2,* which is discussed above.

Scoliosis/Kyphosis

Thirteen individuals had scoliosis; four had kyphosis; three had kyphoscoliosis. Two individuals had congenital kyphoscoliosis, one of whom had C1 and C2 ring fusion and T12 hemivertebrae. One individual had spinal fusion surgery for scoliosis, two had braces with improving results and the rest did not have surgical treatment since in most case the scoliosis was ranging 10 to maximum of 20 degrees.

Seizures

Seizures were not particularly common, but did occur in six individuals. Three individuals had grand mal seizures; two had absence seizures; and one had partial complex seizures. The average age at onset of seizures was 11 years old.

CLOSING THOUGHTS

In the decades since this classic deletion condition was initially identified, much progress has been made. We have been able to establish a fairly complete picture of the phenotype when the deletion breakpoint occurs at the centromere. In addition, great strides have been made in determining which genes on 18p are dosage sensitive. Of the 67 genes on 18p, we think that the majority do not contribute to a phenotype when hemizygous. At this point, we have identified 12 as being either likely or possibly dosage sensitive, though some of those genes would require a second genetic or environmental factor in addition to hemizygosity in order to manifest the phenotype.

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TABLE II. Penetrance for 18p- Phenotypes

Phenotype 18p- (centromere and non-centromere)	Number assessed for each phenotype (homozygous and hemizygous)	Number with phenotype who define critical region	Number hemizygous for critical region (both with and without the phenotype)	% Penetrance
White matter abnormalities (MRI)	52	26	50	52
Ptosis	90	42	89	47
Strabismus	90	34	90	38
Pectus excavatum	83	24	76	32
Scoliosis/Kyphosis	90	20	89	22
Conductive HL	83	18	82	22
Autoimmune disorder	90	12	72	17
Cryptorchidism	44	6	42	14
Pituitary abnormalities (MRI)	54	6	45	13
Seizures	90	7	77	9
Sensorineural HL	83	7	83	8
Sacral agenesis	90	3	41	7
Tetralogy of Fallot	44	3	41	7
Congenital cataracts	90	5	69	7
Hip dysplasia	88	3	67	4

possibly dosage sensitive, though some of those genes would require a second genetic or environmental factor in addition to hemizygosity in order to manifest the phenotype.

Taken together, the information gained from reverse phenotyping as well as the identification of critical regions has enabled us to begin building a molecularly based understanding of 18p-. This information provides a basic framework for the provision of anticipatory guidance to families that are dealing with a new diagnosis. For nearly 50% of patients, the data regarding clinical presentation in centromeric 18p- will help provide anticipatory guidance. In addition, some general recommendations for screenings can be offered, including close monitoring of pituitary function, an echocardiogram to rule out heart disease, regular ophthalmology and audiology evaluations, and referral to early intervention services or other local developmental services at the time of diagnosis. Given that translocations with acrocentric chromosomes are relatively common, we would also recommend that any microarray findings be confirmed by chromosome analysis. Lastly, as direct transmission of a deletion from a parent to a child has been reported, it is reasonable to test the parents, particularly if there is a family history of cognitive impairment, congenital anomalies, or other indications of a chromosome abnormality.

Although the knowledge surrounding 18p- has progressed a great deal since the 1960's, much work remains to be done. As we follow our own study cohort, we will learn more about the implications of 18p- in older individuals. We will also establish whether they are at risk for some of the adult-onset conditions that have recently been linked to 18p, including SCA and FSHD. We will continue to work to understand the effects of hemizygosity of each of the genes located on 18p, a task we are approaching with reverse phenotyping and establishment of critical regions. Ultimately, our goal is to provide genotype-specific anticipatory guidance and recommendations to families with an 18p- diagnosis. In addition, establishing the molecular underpinnings of the condition will potentially suggest targets for molecular treatments.

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