Interstitial Chromosome 3p13p14 Deletions: An Update and Review

Catherine A. Hajek^a Jianling Ji^{b, c} Sulagna C. Saitta^{b, c}

^aSanford Health, and Department of Internal Medicine, University of South Dakota Sanford School of Medicine, Sioux Falls, SD, and ^bCenter for Personalized Medicine, Department of Pathology and Laboratory Medicine, Children's Hospital Los Angeles, and ^cDepartment of Pathology, Keck USC School of Medicine, Los Angeles, CA, USA

Keywords

Chromosomal microarray · 3p13p14 deletions · Structural rearrangements

Abstract

Deletions of proximal chromosome 3p13p14 are infrequent chromosomal alterations. Variable sizes and breakpoints have been reported in patients with a wide range of phenotypes that are evolving as additional cases are reported. The routine use of high-density chromosomal microarrays (CMA) has allowed the identification of many more cases of this disorder and clinical phenotyping shows evidence for an emerging profile among patients with overlapping deletions of 3p13p14. Here, we review the currently reported cases, their phenotypes and where available, the genomic intervals delineated by CMA. Surprisingly, we found that a significant number of proximal chromosome 3p deletions involve structural rearrangements, especially insertions, that have been identified in balanced parental chromosome complements. This region is historically known as a common human chromosomal fragile site, although an underlying genomic mechanism related to its architecture has not been identified. We conclude that identification of an interstitial 3p deletion in a proband by CMA should prompt consider-

ation of further structural chromosomal evaluation using more traditional cytogenetic techniques. While the variability in breakpoints does not suggest a unifying underlying mechanism for these alterations, identification of the haplo-insufficient genes in each patient's deletion interval and their developmental roles can guide genotype-phenotype correlations and impact clinical management.

© 2018 S. Karger AG, Basel

Interstitial deletions of chromosome 3p13p14 are rare chromosome abnormalities, with 43 cases to date reported in the literature [Dimitrov et al., 2015]. Early studies of cytogenetically visible deletions of proximal 3p described patients with a wide range of phenotypes. An initial report from 1979 identified a patient with a 3;18 translocation plus deletion of the 3p13p21 region, who lacked notable anatomic malformations [Kogame and Kudo, 1979]. A subsequent report in 1980 characterized a patient with short stature, microcephaly, microphthalmia, craniofacial dysmorphism, and other congenital malformations with a 3p13p21.1 deletion resulting from a paternal balanced paracentric insertion [Wyandt et al., 1980]. Over the next few years, several patients with a variety of congenital anomalies including cardiac de-

fects, craniofacial dysmorphism, and developmental delays (DD) were published [Sichong et al., 1981], and the delineation of a new proximal 3p deletion syndrome was described [Neri et al., 1984]. In the last decade, the introduction and rapid uptake of high-density oligo-SNP chromosomal microarrays (CMA) led to the identification of more patients with submicroscopic chromosomal copy number alterations and allowed more precise localization of their breakpoints. Approximately half of the reported cases have now been analyzed by CMA across various platforms [de la Hoz et al., 2015; Dimitrov et al., 2015; Hajek et al., 2016]. It has become clear from these reports that the heterozygous deletions are quite variable in size and gene content. Unlike the well-known deletions of chromosomes 7p11.2 (Williams-Beuren syndrome), 15q11.2 (Prader-Willi/Angelman Syndromes), and 22q11.2 Deletion syndrome (DiGeorge/VCFS phenotypes), which are mediated by intrachromosomal segmental duplications, deletions of chromosome 3p13p14 do not appear to have recurrent breakpoints related to nonallelic homologous recombination that results from an underlying genomic architecture. However, complex rearrangements of chromosome 3p, often involving other chromosome partners, have been described. Overall, genotype-phenotype correlation in the proximal 3p deletions is less defined and does not appear to have a clearly delineated “critical” or “core” region. In reviewing these cases, we noted that many of them required adjunct methods such as conventional cytogenetic studies to discern the underlying mechanism. Many required parental analyses to understand the rearrangement in the proband. In this current era of CMA-based diagnosis, we highlight these findings and note that adjunct studies may be required for 3p13p14 deletions, providing data that can impact recurrence risk counseling and prenatal testing for affected families.

Deletion Intervals

Some of the early cases diagnosed by karyotyping include those that extend to the 3p telomere and are not interstitial [Schinzel, 2001]. Among the over 20 cases that were evaluated by CMA, the deletion sizes ranged from large, cytogenetically visible deletions >27 Mb to small submicroscopic deletions <1 Mb [Pariani et al., 2009; Horn et al., 2010; Dimitrov et al., 2015]. The smallest reported deletion involving 3p14 is 498 kb [Horn et al., 2010]. In further reviewing the cases reported by microarray, the deletion intervals varied are listed in Table 1. The

reports which include both published and those in the DECIPHER and ISCA databases are listed chronologically with coordinates aligned to the GRCh37/hg19 version of the genome. These cases show that most were reported to occur de novo in the proband. Prior reports had focused on deletions that included the gene *FOXP1*, which was considered to play a key role in several aspects of the reported phenotype, particularly developmental delay (DD) and intellectual disability (ID). More recently, a group of patients has been described whose deletions are proximal to and do not include *FOXP1*, and while their phenotypes vary, they also display some of the same features as deletions including *FOXP1* (Tables 1, 2).

Figure 1 shows the deletion intervals of 30 cases that had been evaluated by CMA. We noted that chromosome band assignments and coordinates varied slightly depending upon which Human Genome assembly was used. Liftover tools on the UCSC Genome browser site [<http://genome.ucsc.edu>] were used to align all coordinates to assembly hg19 (February 2009), although this may result in chromosome band assignments remaining altered from the initial report.

3p Deletions and Structural Rearrangements

CMA analysis has been widely utilized for several years as the first-tier clinical diagnostic test in patients with unexplained DD/ID, autism spectrum disorders, or multiple congenital anomalies [Miller et al., 2010; Hanemaaijer et al., 2012]. Copy number alteration in the affected individual is usually the initial abnormality detected using this technique. When assessing a copy number loss of this region, there are 2 major reported mechanisms that could potentially lead to a 3p13p14 region deletion. The recurrence risk differs between the 2 scenarios. (1) De novo events: to identify these cases, parental testing can be performed using CMA or classical cytogenetic techniques such as FISH, and/or chromosomal studies if the size of the deletion is large enough to be identified in a karyotype [Youings et al., 2004]. (2) Predisposing parental structural abnormalities: these include rare balanced insertional translocations, which can be missed if CMA alone is used for follow-up parental studies [Hajek et al., 2016]. Since CMA does not provide structural information and primarily determines copy number, a balanced rearrangement may not be identified in a carrier parent and may be mistakenly considered as a de novo alteration in the affected child with a negligible recurrence risk for future pregnancies. In the era of CMA, FISH analysis is a

Table 1. Summary of 3p13 or 3p14 deletion cases published in the literature or databases

Year published	Reference paper	Coordinates (GRCh37/hg19)	Chromosome band		Size, Mb	Inherited or de novo	Key genes
			hg18	hg19			
1979	Kogame and Kudo	NA	3p13p21		NA	unknown	NA
1980	Wyandt et al.	NA	3p13.5p21.1		NA	paternal paracentric inverted insertion 46,XY,ins(3)(p25.5p21.1p13.5)	NA
1981	Sichong et al.	NA	3p11p14.2		NA	de novo	NA
1984	Neri et al.	NA	3p12p14.2		NA	presumably de novo (normal parental karyotype)	NA
1984	Mitter et al.	NA	3p13p21		NA	presumably de novo (normal parental karyotype)	NA
1986	Short et al.	NA	3p13.2p21		NA	de novo	NA
1988	Hertz et al.	NA	3p11p14.2		NA	presumably de novo (normal parental karyotype)	NA
1988	Naritomi et al.	NA	3p12p14.2		NA	de novo	NA
1995	Crispino et al.	NA	3p11p14.1		NA	unknown (normal maternal karyotype, father not available for testing)	NA
1997	Wieczorek et al.	NA	3p12p21.2		NA	presumably de novo (normal parental karyotype)	NA
1998	Pfeiffer et al.	NA	3p12.1p21.31		NA	paternal paracentric insertion: 46,XY,ins(3)(p24.1p12.1p21.31)	NA
2003	Petek et al.	NA	3p11p13		~15	de novo	FOXPI, PROK2, GPR27, RYBP, PPP4R2, ROBO1, GBE1
2007	Schwarzbraun et al.	NA	3p12.2p14.1		NA	de novo	MITF, FOXPI, TMF1, RYBP, ROBO1
2009	Pariani et al.	chr3:71081471 – 71876155	3p13p14.1	3p13	0.785	de novo	FOXPI, EIF4E3, PROK2, GPR27
2009	Morales et al.	chr3:73117310 – 78917310	3p12.3p13	3p12.3p13	5.8	de novo	ROBO1, ROBO2, PDZRN3, and CNTN3
2010	Carr et al.	chr3:70467233 – 71535980	3p14.1	3p13	1.1	de novo	FOXPI
2010	Horn et al., P1	chr3:70725077 – 71223275	3p14.1	3p13	0.498	unknown	FOXPI
2010	Horn et al., P2	chr3:70695380 – 71354664	3p14.1	3p13	0.659	de novo	FOXPI
2010	Horn et al., P3	chr3:70258557 – 71305483	3p14.1	3p13	1.046	de novo	FOXPI
2011	Tao et al.	chr3:62690487 – 64915076	3p14.1p14.2	3p14.1p14.2	2.2	unknown	PRICKLE2
2012	Tuñulan-Cunità et al.	chr3:65342824 – 77820255	3p12.3p14.1	3p12.3p14.1	12.5	unknown	31 ORFs, among which ROBO2, PDZRN3, MITF, and FOXPI
2013	Le Fevre et al.	chr3:71041636 – 71229421	3p13	3p13	190 kb	de novo	FOXPI
2013	Schwaibold et al.	chr3:58244794 – 64571699	3p14.1p14.3	3p14.1p14.3	6.32	presumably de novo (normal parental aCGH)	FHIT, PTPRG, FEZF2, CADPS, SYNPR, ATXN7, PRICKLE2
2013	Schwaibold et al.	chr3:59443171 – 64162112	3p14.1p14.2	3p14.1p14.2	4.76	unknown	FHIT, PTPRG, FEZF2, CADPS, SYNPR, ATXN7, PRICKLE2
2013	Palumbo et al.	chr3:70429306 – 71437677	3p14.1	3p13	1	presumably de novo (normal parental SNP-array)	FOXPI

Table 1 (continued)

Year published	Reference paper	Coordinates (GRCh37/hg19)	Chromosome band		Size, Mb	Inherited or de novo	Key genes
			hg18	hg19			
2014	Thevenon et al., P1	chr3:71006071–73344433		3p13	2.33	de novo	FOXPI, EIF4E3
2014	Thevenon et al., P2	chr3:71540307–82716711		3p12.2p13	11.18	unknown	FOXPI, EIF4E3
2014	Thevenon et al., P3	chr3:68541944–72842054		3p13p14.1	4.3	de novo	FOXPI, EIF4E3
2014	Thevenon et al., P4	chr3:71366497–74373822		3p12.3p13	3.01	de novo	FOXPI, EIF4E3
2014	Dimitrov et al., P1	chr3:58598577–74508971		3p12.3p14.2	16	de novo	50 known genes
2014	Dimitrov et al., P2	chr3:59703992–86824958		3p12.1p14.2	27.2	unknown	61 known genes
2014	Dimitrov et al., P3	chr3:62046934–77330720		3p12.3p14.2	15.4	unknown	53 known genes
2014	Lloveras et al.	chr3:64070656–77810556		3p12.3p14.1	13.7	paternal insertional translocation: 46,XY,ins(3)(p25p12.3p14.1)	ROBO2, CNTN3, PROK2, PDZRN3, MIF, FOXPI
2014	Okumura et al.	chr3:60472496–67385119		3p14.1p14.2	6.88	de novo	FEZF2, SYNPR, ATXN7, PRICKLE2, MAGI1
2015	de la Hoz et al.	chr3:60461316–68515453		3p14.1p14.2	8	de novo	FEZF2, CADPS, SYNPR, ATXN7, PRICKLE, and MAGI
2016	Hajek et al.	chr3:59854516–75236053		3p12.3p14.2	15.4	maternal insertional translocation: 46,XX,ins(18;3)(q12.2p12.3p14.2)	FOXPI, MIF, CADPS, CNTN3, SYNPR, FEZF2, PDZRN3, and ATXN7
	Decipher 2250	chr3:54452525–65609348		3p14.1p14.3	11.16	de novo	FHIT, PTPRG, FEZF2, CADPS, SYNPR, ATXN7, PRICKLE2
	Decipher 250453	chr3:58717185–61696115		3p14.2	2.98	inherited from normal parent?	FHIT, PTPRG
	Decipher 255918	chr3:62749576–63021934		3p14.2	0.272	unknown	CADPS
	Decipher 260004	chr3:59813606–65296648		3p14.1p14.2	5.48	de novo	FHIT, PTPRG, FEZF2, CADPS, SYNPR, ATXN7, PRICKLE2
	ISCA nssv1605032	chr3:57416265–64870197		3p14.1p14.3	7.45	unknown	FHIT, PTPRG, FEZF2, CADPS, SYNPR, ATXN7, PRICKLE2
	ISCA nssv577902	chr3:54079045–66046136		3p14.1p21.1	11.97	de novo	FHIT, PTPRG, FEZF2, CADPS, SYNPR, ATXN7, PRICKLE2
	ISCA nssv577904	chr3:61956521–68514983		3p14.1p14.2	6.56	de novo	PTPRG, FEZF2, CADPS, SYNPR, ATXN7, PRICKLE2

When necessary, genomic coordinates were converted from hg18 to hg19 builds using the UCSC Genome Browser LiftOver tool with standard parameters. In cases with provided genomic coordinates of both maximal and minimal deleted region in the original article, coordinates for the minimal deletion region are listed. In cases with array CGH results based on an hg18 build, chromosome bands in both hg18 and hg19 builds are listed in the table. For cases that were analyzed by karyotype and not array, NA has been entered in the Coordinates column. P, patient.

Table 2. Phenotype summary of 3p deletion cases involving 3p13 or 3p14 published in the literature and databases

Year published	Reference paper	DD/ID	Autism	Facial dysmorphism	Limb abnormalities	Size, Mb
Cases with cytogenetically visible deletions						
1979	Kogame and Kudo	+	NM	hypertelorism, downslanting palpebral fissures, saddle nose, low-set ears, high-arched palate	clinodactyly, thin extremities, overlapping toes	NA
1980	Wyandt et al.	+	NM	microcephaly, high prominent forehead, epicanthal folds, short palpebral fissures, ptosis of upper eyelids	short 5th metacarpals, clubbing of nails, limited extension of hips	NA
1981	Sichong et al.	+	NM	high and broad forehead, narrow palpebral fissures, epicanthal folds, synophrys, broad and flat nasal ridge, anteverted nostrils, dysplastic and low-set ears, high-arched palate	bilateral ulnar deviation of the hands, restricted flexion and extensions of the wrists, transverse palmar crease bilaterally, mild pes equinovarus	NA
1984	Neri et al.	NM	neurologically normal	dolichocephalic, hypoplastic supraorbital ridge, broad nasal bridge, epicanthal folds, small ears with hypoplastic lobules and posterior angulation, small mouth, micrognathia	decreased supination of forearms and ulnar deviation of hands, overlapping fingers, camptodactyly, decreased extension of knees, decreased abduction at the hips, broad great toes	NA
1986	Short et al.	NA	NA	multiple deformities noted	NM	NA
1988	Hertz et al.	NA	NA	long narrow cranium with high broad forehead, hypertelorism, epicanthal folds, short broad nose, broad nasal bridge, anteverted nostrils, large philtrum, low-set posteriorly rotated ears,	ulnar deviation of wrists, single flexion crease in left hand	NA
1988	Naritomi et al.	+	NA	left eyelid ptosis, high broad forehead, hypoplastic supraorbital ridges, prominent lymphedematous swelling of the upper eyelids, narrow downslanting palpebral fissures, epicanthal folds, broad flat nasal bridge with bulbous tip, low-set ears, high-arched narrow palate, micrognathia	clenched fingers, camptodactyly, overlapping thumbs and fingers, widely spaced 1st and 2nd toes	NA
1995	Crispino et al.	NM	NM	full cheeks, hypertelorism, broad and flat nasal bridge, epicanthal folds, posteriorly angulated ears	small hands, bilateral ulnar deviation at wrist, adducted thumbs, hypoplastic thenar and hypothenar eminences, limited movement in finger joints	NA
1997	Wieczorek et al.	+	NM	broad forehead with low frontal hairline, short broad-based nose with anteverted nostrils, low-set abnormal left ear, hypertelorism, bilateral micropthalmia, full cheeks, micrognathia, short philtrum, high palate	decreased knee extension, camptodactyly of 2nd fingers, overlapping fingers, ulnar deviation of hands	NA
1998	Pfeiffer et al.	NA	NA	low-set ears	short fingers	NA
2003	Petek et al.	+	NM	isolated lateral cleft lip, downslanting palpebral fissures, square facies with wide forehead, hypoplastic supraorbital ridges, arched eyebrows, short nose, low-set posteriorly angulated ears, short neck	NM	~15
2007	Schwarzbraun et al.	+	NM	small low-set ears with over folded helix, micro/retrognathia, midface hypoplasia	NM	NA

Table 2 (continued)

Year published	Reference paper	DD/ID	Autism	Facial dysmorphism	Limb abnormalities	Size, Mb
Cases reported by microarray						
	Decipher 255918	+	NM	plagiocephalus	syndactyly of 2nd and 3rd toes	0.272
2010	Horn et al., P1	+	NM	no dysmorphism	NM	0.498
2010	Horn et al., P2	+	NM	prominent forehead, frontal hair upsweep	NM	0.659
2009	Pariani et al.	+	NM	blepharophimosis, epicanthal folds, small upturned alae nasi, prominent cheeks	severe contractures of hands and feet	0.785
2013	Palumbo et al.	+	+	hypotonic long face, broad and prominent forehead, palpebral ptosis, downslanting palpebral fissures, open mouth, thick lips, abnormal tooth position, malocclusion, open bite, pointed chin	NM	1
2010	Horn et al., P3	+	NM	prominent forehead, frontal hair upsweep	NM	1.046
2010	Carr et al.	+	NM	left puffy face	NM	1.1
2011	Tao et al.	+	+	NM	NM	2.2
2014	Thevenon et al., P1	+	NM	hypertelorism, high palate, low-set and posteriorly rotated ears	ulnar deviation of wrists, finger immobility	2.33
	Decipher 250453	+	NM	low frontal hairline, prominent mandible, wide-spaced teeth, low-set posteriorly rotated simple ears	none	2.98
2014	Thevenon et al., P4	+	NM	hypotelorism, ptosis, epicanthal folds, mild clinical microphthalmia, low-set and posteriorly rotated ears, small mouth	bilateral clinodactyly of toes III, IV, and V	3.01
2013	Schwaibold et al.	+	+	broad mouth, prominent chin, widely spaced teeth, deep-set eyes, long slender face, flat occiput	high tonicity in lower limbs	4.76
	Decipher 260004	+	NM	prominent forehead, frontal bossing, low-set posteriorly rotated ears	clinodactyly	5.48
2009	Morales et al.	+	NM	broad forehead, hypertelorism broad nasal bridge, microretrognathia, pointed chin	clinodactyly	5.8
2013	Schwaibold et al.	+	+	arched downslanting eyebrow, plagiocephalus, low-set posteriorly rotated ears	twin B: thick left thumb with sites for 2 nails	6.32
	ISCA nssv577904	NA	NA	NA	NA	6.56
2014	Okumura et al.	+	+	arched downslanting eyebrow, prominent forehead, epicanthic folds, micrognathia, hypertelorism, broad nasal bridge, short philtrum	camptodactyly	6.91
	ISCA nssv1605032	NA	NA	NA	NA	7.45
2015	de la Hoz et al.	+	+	long face, prominent chin, broad forehead, wide mouth, widely spaced upper front teeth, slightly large and detached ears	none	8
	Decipher 2250	+	NM	arched thick eyebrows, macrostomia, epicanthic folds, wide forehead, high palate	camptodactyly, club foot, valgus, ulnar deviation of hand	11.16

Table 2 (continued)

Year published	Reference paper	DD/ID	Autism	Facial dysmorphism	Limb abnormalities	Size, Mb
2014	Thevenon et al., P2	NM	NM	NM	club feet, bilateral hip dislocation	11.18
	ISCA nssv577902	NA	NA	NA	NA	11.97
2012	Țuțulan-Cunită et al.	+	NM	square face, broad forehead, short palpebral fissures, broad nasal bridge, epicanthic folds, short philtrum, small dysplastic low-set ears	small short fingers, overlapping toes, spastic diparesis	12.5
2014	Lloveras et al.	+	NM	short neck, low posterior hairline	total syndactyly of the 3rd and 4th toes	13.7
2016	Hajek et al.	+	NM	bilateral frontal hair whorls on forehead, prominent bossed forehead, pinched nasal bridge, small eyelids with shortened palpebral fissures, blepharophimosis, left microphthalmia, downturned mouth, high-arched palate, micrognathia, right ear with poorly formed helix	hypoplastic thumbs, bilateral club feet, clenched and contracted hands, clenched toes	15.4
2014	Dimitrov et al., P3	NM	NM	hypertelorism, bilateral iris coloboma, flat nasal bridge, short philtrum, cup-shaped ears	clenched hands with ulnar deviation, unilateral single palmar crease, bilateral under-riding 3rd toe	15.4
2014	Dimitrov et al., P1	+	+	wide nasal bridge, hypertelorism, abnormal ears with prominent inferior crus and step of the antihelix, underdeveloped superior crus of the helix, downslanting palpebral fissures, hypertelorism, bilateral aniridia, small mouth	bilateral camptodactyly, flexion deformity of fingers, single palmar creases, wide sandal gap bilaterally	16
2014	Dimitrov et al., P2	NM	NM	broad forehead with low frontal hairline, hypertelorism, short and broad nose with anteverted nares, short philtrum, right choanal atresia, bilateral microphthalmia and iris coloboma, small low-set ears, high palate, micrognathia	bilateral ulnar deviation of hands, bilateral single palmar creases, camptodactyly, wide sandal gap in both feet	27.2
2013	Le Fevre et al.	+	NM	prominent forehead, downslanting palpebral fissures, flat malar region, short nose with broad tip	prominent digit pads, clinodactyly of 4th toes bilaterally	190 kb

Results from the array CGH were converted from hg18 to hg 19 builds using the LiftOver tool with standard parameters. Carr et al. used coordinates for the minimal deleted region. Coordinates of minimal deleted region were used in the table. DD, developmental delay; ID, intellectual disability; NA, not available; NM, not mentioned; P, patient; +, present.

Fig. 1. Cases of 3p deletions involving chromosome band 3p13 or 3p14. A total of 30 cases of 3p13 or 3p14 deletions whose array coordinates were published or listed in the DECIPHER database are depicted superimposed on the UCSC genome browser. The coordinates were converted to the Human GRCh37/hg19 assembly from February 2009.

technique that may be overlooked, nonetheless it can be very helpful in detecting the parental origin of a patient's chromosomal deletion and determining its underlying mechanism. Specifically, metaphase FISH studies using a probe from within the deletion interval would provide an appropriate approach to identify or to exclude parental structural abnormalities. In certain circumstances, when the deletion is large enough (generally >5–10 Mb), a parental karyotype study alone may identify balanced structural abnormalities.

Indeed, the published literature reports a number of cases of interstitial proximal chromosome 3p deletions that involve structural rearrangements; they are listed in Table 3.

Of the reported deletions, we note that at least 6 involve structural rearrangements, with 4 determined to result from underlying balanced, often complex insertional rearrangements in a carrier parent. In general, the frequency of insertions has been estimated at approximately

1:80,000 patients based on karyotyping alone [Van Hemel and Eussen, 2000]. However, a more recent study in which 18,000 cases were evaluated revealed that the frequency of insertions was approximately 1:450 when using newer molecular cytogenetic techniques [Kang et al., 2010]. Given that at least 6/43 cases (14%) showed predisposing structural findings, adjunct testing of parents should be considered in cases of proximal 3p deletion in order to more accurately define the recurrence risk. Indeed, this number may be underestimated since many published studies used CMA as the only technique for parental follow-up testing. Additionally, not all parents were available and studied for each case.

The chromosome 3p14 region of the genome has long been known as a common fragile site (CFS), or a locus where recurrent breaks, gaps, and constrictions can be seen in metaphase chromosomes when cells are subjected to replication stress [Debatisse et al., 2012]. CFS, which are devoid of mini or microsatellite repeats, appear to be

Table 3. Chromosome 3p proximal deletions involving structural rearrangements

3p deletions in proband	Parental balanced structural chromosomal abnormality	Reference
46,XY,der(3)del(3)(p11p14.1)t(3;20)(p14.1;p12.2),der(20)t(3;20)	mother: 46,XX father: not available	Crispino et al., 1995
46,XY,der(3)del(3)(p13p21)t(3;18)(p13;q23),der(18)t(3;18)	unknown	Kogame and Kudo, 1979
46,XX,del(3)(p12.1p21.31)	paternal paracentric insertion 46,XY,ins(3)(p24.1p12.1p21.31)	Pfeiffer et al., 1998
46,XY,del(3)(p13p21.1)	paternal paracentric inverted insertion 46,XY,ins(3)(p25p12.1p13)	Wyandt et al., 1980
46,XY,del(3)(p12p14)	maternal balanced insertion 46,XX,ins(18;3)(q12.2;p12.3p14.2)	Hajek et al., 2016
46,XX,del(3)(p12.3p14.1)	paternal intrachromosomal insertion 46,XY,ins(3)(p25p12.3p14.1) note: sibling with reciprocal duplication of proband	Lloveras et al., 2014

present in all individuals of a population, but the expression or frequency of breakage can differ. In human lymphocytes, the *FRA3B* site is the most fragile CFS reported and localizes to a 1.6-Mb region of chromosome 3p14.2 within the *FHIT*, fragile histidine triad gene, where approximately 85% of the CFS breaks occur [Debatisse et al., 2012]. Further molecular analysis described in that study showed that a paucity of initiation sites, which subsequently increases the length of replication-fork traveling, plays a major role in CFS instability. Similar studies in yeast have noted that reduction of replication initiation efficiency in initiation-poor sites would lead to an increase in chromosome rearrangements. Indeed, early cytogenetic reports noted that this most commonly observed human fragile site in 3p14 was frequently involved in chromosomal aberrations found in tumors, though it was not thought to be a common site for constitutional rearrangements [Hecht, 1988; Murata et al., 1992]. However, the localization of this common human fragile site and the occurrence of complex constitutional rearrangements, insertions, and deletions is an intriguing finding, suggesting that the underlying structure of this chromosomal region could be associated with a predisposition to rearrangement. In recurrent genomic disorders such as those of chromosome 22q11.2, the sizes and gene content of the deletions are the same in unrelated individuals, and the underlying mechanism is related to intrachromosomal segmental duplications or low copy repeats, where significant stretches of >90% homology in the duplications mediate nonallelic homologous recombination [Carval-

ho and Lupski, 2016]. Instead, the 3p13p14 deletions show different sizes and gene content from individual to individual. To our knowledge, specific breakpoints have not been characterized at the sequence level for these deletions; however, in other nonrecurrent deletions, small insertions have been identified at the junctions and experimental observations suggest that regions of microhomology are involved in the rearrangement mechanisms [Carvalho and Lupski, 2016].

Specific Genes and Contribution to Phenotype

Chromosome 3p deletions show multiple breakpoints with varied genes included in each patient's deletion interval. As expected, the phenotypes also vary, but there are some overlapping clinical features including DD/ID, autism, craniofacial dysmorphism, and limb abnormalities. The reports of additional system involvement vary. The reported deletions represent an emerging phenotype more readily defined with the use of CMA and reflect the haploinsufficiency of several distinct genes that likely contribute to the associated malformations and developmental issues encountered in the patients.

In a series of 14 patients with proximal interstitial 3p deletions, several similar phenotypic features were described [Dimitrov et al., 2015]. Table 2 summarizes the findings in 41 cases from the literature showing several of the key features and deletion intervals of these cases. The overlapping features are consistent with the previously

published series from Dimitrov et al. [2015] and include prominent forehead, short palpebral fissures, hand and foot anomalies, autism, and DD/ID. The clinical similarity of these cases together with the significant overlap of the deleted regions suggests that the deletion of specific genes within the region correlate with specific features.

Below, we summarize the potential contributions of several genes felt to be key to the clinical findings in the patients who harbor deletions that include each of these genes.

FOXP1

The *FOXP1* gene (OMIM 613670) has been associated with multiple deletions involving this region in patients with ID and DD. In 2013, Le Fevre et al. described a single patient and literature review of several others with *FOXP1* deletions and severe ID/DD as well as severe speech delay, with particular deficits of expressive speech. A prior case described a 1.0-Mb interstitial deletion of 3p14.1 that only involved the *FOXP1* gene in a patient with speech and motor delays, a Chiari I malformation, and epileptiform activity [Carr et al., 2010]. An additional report described 3 de novo heterozygous overlapping deletions each involving only *FOXP1* [Horn et al., 2010]. All 3 patients had moderate ID and significant language and speech deficits. A de novo intragenic deletion encompassing exons 4–14 of *FOXP1* was found in a patient with nonsyndromic ID and autistic features [Hamdan et al., 2010]. Formal assessments noted severe language impairment, mood lability with aggression and specific obsessions as well as compulsions. These cases support haploinsufficiency of *FOXP1* as a significant contributor to the phenotype and disease mechanism of patients with larger 3p deletions that also include this gene [Tuțulan-Cunită et al., 2012].

MITF

Another important feature described in several cases of interstitial deletions of 3p is sensorineural hearing loss, which has been attributed to haploinsufficiency of the *MITF* gene (OMIM 156845) at 3p13p14.1, a gene considered causal for Waardenberg syndrome Type 2A (WS2A) hearing loss [Nobukuni, 1996]. Full or partial gene deletions and truncating mutations in *MITF* have been previously described as disease-causing for WS2A, an autosomal dominant disorder [Milunsky et al., 2007; Pingault et al., 2010]. Both *FOXP1* and *MITF* are genes likely to exhibit haploinsufficiency based on their DECIPHER haploinsufficiency scores of 0.13 and 0.97, respectively. A second database ClinGen (<https://www.ncbi.nlm.nih.gov/projects/dbvar/clingen>) assigns a score of 3 for both

genes. This score provides a loss-of-function rating from 0 to 3, with higher ratings reflecting increasing levels of evidence that suggest dosage sensitivity is related to a given phenotype. Inclusion of *MITF* within a patient's deletion further underscores the need for careful screening and sequential developmental follow-up and intervention for these affected patients.

PROK2

This gene encodes prokineticin 2, a rhythmically expressed protein by the suprachiasmatic nucleus circadian clock that appears to have a developmental role in neuronal migration. Both homozygous and heterozygous point mutations in *PROK2* have been associated with hypogonadotropic hypogonadism type 4 with or without anosmia, which is part of the Kallmann syndrome disease spectrum (OMIM 610628). Of note, putative heterozygous truncating mutations have been reported, supporting a haploinsufficiency mechanism of disease.

ATXN7

This gene encodes ataxin 7, a transcription factor that plays a significant role in chromatin remodeling. Alterations in *ATXN7* are associated with the autosomal dominant neurodegenerative disorder spinocerebellar ataxia 7, an adult-onset disorder that features progressive cerebellar ataxia and pigmentary macular degeneration (OMIM 164500). The mechanism of disease is an unstable expansion of a (CAG)_n repeat from a range of 7–17 repeats in normal alleles with variable expansion up to 38–130 repeats in affected patients. As described in other translated polyglutamine triplet repeat disorders, the repeat tracts are unstable with transmission, and the expansion is associated with anticipation seen in subsequent affected generations. There is striking gonadal instability upon paternal transmission. However, haploinsufficiency of *ATXN7* caused by a 3p14 deletion has not been associated with this disorder or with any other known clinical entity to date.

FHIT

The fragile histidine triad or *FHIT* gene encodes an AP3A hydrolase and was initially identified by its location at a renal cell carcinoma t(3;8) breakpoint. It is known to span the chromosome 3p14 fragile site, FRA3B [Ohta et al., 1996]. Subsequently, a 200 to 300-kb region including FRA3B was found to be homozygously deleted in multiple tumor cell lines with aberrant *FHIT* transcripts found in up to 50% of esophageal, colon, and stomach cancers [Ohta et al., 1996]. Somatic mutations of *FHIT* have also been described in several other tumors (OMIM 601153),

though to date, constitutional alterations in *FHIT* have not been associated with a known developmental phenotype. In addition, there have not been reports of a significantly increased cancer risk in patients with chromosome 3p14 deletions.

The varied deletions described in patients with 3p deletion syndromes include other genes, many of which have not yet been associated with a specific human disorder. It will be important to determine the contribution of these other potential neurodevelopmental genes toward DD and ID. Genes that are found in the deletions of multiple patients include *CADPS*, *CNTN3*, *FEZF2*, *PDZRN3*, *MAGI1*, and *PRICKLE2* [Tao et al., 2011; Schwaibold et al., 2013; de la Hoz et al., 2015; Dimitrov et al., 2015]. To date, they are not clearly associated with a clinical phenotype nor are they designated OMIM morbid genes, but their tissue distribution and putative function make them interesting candidates for future studies and genotype-phenotype correlations.

Conclusion

Overall, the recent adoption of high-density oligo-SNP CMA has led to the increased identification of cases of chromosome 3p13p14 deletion syndrome. A significant number of these deletions result from complex rearrangements, particularly insertions, which can be found in a balanced state in a carrier parent and prompts the use of structural cytogenetic techniques to identify them. The phenotypes, while varied, do consistently show neurodevelopmental effects, and several specific genes have been determined to be responsible for key clinical features in the patients. Further studies of the underlying structure of the region and examination of the breakpoints of the complex rearrangements that result in 3p deletions may aid in better understanding their genomic mechanisms. Likewise, functional studies of the less well-studied genes located in the deleted intervals can help to elucidate their roles in patient phenotypes and help guide better clinical management and treatment.

References

- Carr CW, Moreno-De-Luca D, Parker C, Zimmerman HH, Ledbetter N, et al: Chiari I malformation, delayed gross motor skills, severe speech delay, and epileptiform discharges in a child with *FOXP1* haploinsufficiency. *Eur J Hum Genet* 18:1216–1220 (2010).
- Carvalho CM, Lupski JR: Mechanisms underlying structural variant formation in genomic disorders. *Nat Rev Genet* 17:224–238 (2016).
- Crispino B, Cardoso H, Mimbacas A, Méndez V: Deletion of chromosome 3 and a 3;20 reciprocal translocation demonstrated by chromosome painting. *Am J Med Genet* 55:27–29 (1995).
- Debatisse M, Le Tallec B, Letessier A, Dutrillaux B, Brison O: Common fragile sites: mechanisms of instability revisited. *Trends Genet* 28:22–32 (2012).
- de la Hoz AB, Maortua H, Garcia-Rives A, Martinez-Gonzalez MJ, Ezquerro M, Tejada MI: 3p14 de novo interstitial microdeletion in a patient with intellectual disability and autistic features with language impairment: a comparison with similar cases. *Case Rep Genet* 2015:876348 (2015).
- Dimitrov BI, Ogilvie C, Wiczorek D, Wakeling E, Sikkema-Raddatz B, et al: 3p14 deletion is a rare contiguous gene syndrome: report of 2 new patients and an overview of 14 patients. *Am J Med Genet A* 167:1223–1230 (2015).
- Hajek C, Wang JC, Mahon LW, Martinez A, Saita SC: Interstitial chromosome 3p14.1 deletion due to a maternal translocation: phenotype and association with balanced parental rearrangement. *Mol Syndromol* 7:43–48 (2016).
- Hamdan FF, Daoud H, Rochefort D, Piton A, Gauthier J, et al: De novo mutations in *FOXP1* in cases with intellectual disability, autism, and language impairment. *Am J Hum Genet* 87:671–678 (2010).
- Hanemaaijer N, Sikkema-Raddatz B, van der Vries G, Dijkhuizen T, Hordijk R, et al: Practical guidelines for interpreting copy number gains detected by high-resolution array in routine diagnostics. *Eur J Hum Genet* 20:161–165 (2012).
- Hecht F: Rare and polymorphic fragile sites and cancer. *Cancer Genet Cytogenet* 34:195–199 (1988).
- Hertz JM, Coerdts W, Hahnemann N, Schwartz M: Interstitial deletion of the short arm of chromosome 3. Fetal pathology and exclusion of the gene for beta-galactosidase-1 (GLB-1) from 3(p1-p14.2). *Hum Genet* 79:389–391 (1988).
- Horn D, Kapeller J, Rivera-Brugués N, Moog U, Lorenz-Depiereux B, et al: Identification of *FOXP1* deletions in three unrelated patients with mental retardation and significant speech and language deficits. *Hum Mutat* 31:E1851–E1860 (2010).
- Kang SH, Shaw C, Ou Z, Eng PA, Cooper ML, et al: Insertional translocation detected using FISH confirmation of array-comparative genomic hybridization (aCGH) results. *Am J Med Genet A* 152A:1111–1126 (2010).
- Kogame K, Kudo H: Interstitial deletion 3p associated with t(3p;18q+) translocation. *Jinrui Idengaku Zasshi* 24:245–252 (1979).
- Le Fevre AK, Taylor S, Malek NH, Horn D, Carr CW, et al: *FOXP1* mutations cause intellectual disability and a recognizable phenotype. *Am J Med Genet A* 161A:3166–3175 (2013).
- Lloveras E, Vendrell T, Fernández A, Castells N, Cueto A, et al: Intrachromosomal 3p insertion as a cause of reciprocal pure interstitial deletion and duplication in two siblings: further delineation of the emerging proximal 3p deletion syndrome. *Cytogenet Genome Res* 144:290–293 (2014).
- Miller DT, Adam MP, Aradhya S, Biesecker LG, Brothman AR, et al: Consensus statement: chromosomal microarray is a first-tier clinical diagnostic test for individuals with developmental disabilities or congenital anomalies. *Am J Hum Genet* 86:749–764 (2010).
- Milunsky J, Maher TA, Ito M, Milunsky A: The value of MLPA in Waardenburg syndrome. *Genet Test* 11:179–182 (2007).
- Mitter NS, Bryke CR, Sunderji SG, Hallinan EJ, Gordon LP: Prenatal diagnosis of interstitial deletion of short arm of chromosome 3. *Am J Hum Genet* 36:105A (1984).

- Morales C, Mademont-Soler I, Armengol L, Milà M, Badenas C, et al: Characterization of a 5.8-Mb interstitial deletion of chromosome 3p in a girl with 46, XX, inv(7)dn karyotype and phenotypic abnormalities. *Cytogenet Genome Res* 125:334–340 (2009).
- Murata M, Otsuka M, Hayakawa Y, Takahashi E, Tsuji H, Hori T: Expressivity of a common fragile site, fra (3)(p14), in patients with cancer and other diseases. *Jpn J Hum Genet* 3: 205–213 (1992).
- Naritomi K, Hirayama K, Sameshima K, Ohdo S: Proximal 3p deletion: case report and review of the literature. *Acta Paediatr Jpn* 30:78–83 (1988).
- Neri G, Reynolds JF, Westphal J, Hinz J, Daniel A: Interstitial deletion of chromosome 3p: report of a patient and delineation of a proximal 3p deletion syndrome. *Am J Med Genet* 19:189–193 (1984).
- Nobukuni Y, Watanabe A, Takeda K, Skarka H, Tachibana M: Analyses of loss-of-function mutations of the *MITF* gene suggest that haploinsufficiency is a cause of Waardenburg syndrome type 2A. *Am J Hum Genet* 59:76–83 (1996).
- Ohta M, Inoue H, Cotticelli MG, Kastury K, Baffa R, et al: The *FHIT* gene, spanning the chromosome 3p14.2 fragile site and renal carcinoma-associated t(3;8) breakpoint, is abnormal in digestive tract cancers. *Cell* 84:587–597 (1996).
- Okumura A, Yamamoto T, Miyajima M, Shimajima K, Kondo S, et al: 3p interstitial deletion including *PRICKLE2* in identical twins with autistic features. *Pediatr Neurol* 51:730–733 (2014).
- Palumbo O, D'Agruma L, Minenna AF, Palumbo P, Stallone R, et al: 3p14.1 de novo microdeletion involving the *FOXP1* gene in an adult patient with autism, severe speech delay and deficit of motor coordination. *Gene* 516:107–113 (2013).
- Pariani M, Spencer A, Graham JM Jr, Rimoin DL: A 785 kb deletion of 3p14.1p13, including the *FOXP1* gene, associated with speech delay, contractures, hypertonía and blepharophimosis. *Eur J Med Genet* 52:123–127 (2009).
- Petek E, Windpassinger C, Simma B, Mueller T, Wagner K, Kroisel PM: Molecular characterization of a 15 Mb constitutional de novo interstitial deletion of chromosome 3p in a boy with developmental delay and congenital anomalies. *J Hum Genet* 48:283–287 (2003).
- Pfeiffer RA, Rauch A, Ulmer R, Beinder E, Trautmann U: Interstitial deletion del(3)(p12p21) in a malformed child subsequent to paternal paracentric insertion (or intraarm shift) 46, XY, ins(3)(p24.1p12.1p21.31). *Ann Genet* 41: 17–21 (1998).
- Pingault V, Ente D, Dastot-Le Moal F, Goossens M, Marlin S, Bondurand N: Review and update of mutations causing Waardenburg syndrome. *Hum Mutat* 31:391–406 (2010).
- Schinzel A: Catalogue of Unbalanced Chromosome Aberrations in Man, ed 2 (de Gruyter, Berlin, New York 2001).
- Schwaibold EMC, Zoll B, Burfeind P, Hobbiebrunken E, Wilken B, et al: A 3p interstitial deletion in two monozygotic twin brothers and an 18-year-old man: further characterization and review. *Am J Med Genet A* 161: 2634–2640 (2013).
- Schwarzbraun T, Ofner L, Gillessen-Kaesbach G, Schaperdorth B, Preisegger KH, et al: A new 3p interstitial deletion including the entire *MITF* gene causes a variation of Tietz/Waardenburg type IIA syndromes. *Am J Med Genet A* 143A: 619–624 (2007).
- Short MP, Shah KD, Djamdjian S, Dische MR, Gilbert F: Interstitial deletion of the short arm of chromosome 3, 3p14. *Am J Med Genet* 24A: 649–652 (1986).
- Sichong Z, Bui TH, Castro I, Iselius L, Håkansson S, Lundmark KM: A girl with an interstitial deletion of the short arm of chromosome 3 studied with a high-resolution banding technique. *Hum Genet* 59:178–181 (1981).
- Tao H, Manak JR, Sowers L, Mei X, Kiyonari H, et al: Mutations in prickle orthologs cause seizures in flies, mice, and humans. *Am J Hum Genet* 88:138–149 (2011).
- Thevenon J, Monnier N, Callier P, Dieterich K, Francoise M, et al: Delineation of the 3p14.1p13 microdeletion associated with syndromic distal limb contractures. *Am J Med Genet A* 164A:3027–3034 (2014).
- ȚuȚulan-Cunită AC, Papuc SM, Arghir A, Rötzer KM, Deshpande C, et al: 3p interstitial deletion: novel case report and review. *J Child Neurol* 27:1062–1066 (2012).
- Van Hemel JO, Eussen HJ: Interchromosomal insertions: identification of five cases and a review. *Hum Genet* 107:415–432 (2000).
- Wieczorek D, Bolt J, Schwechheimer K, Gillessen-Kaesbach G: A patient with interstitial deletion of the short arm of chromosome 3 (pter→p21.2::p12→qter) and a CHARGE-like phenotype. *Am J Med Genet* 69A:413–417 (1997).
- Wyandt HE, Kasprzak R, Ennis J, Willson K, Koch V, et al: Interstitial 3p deletion in a child due to paternal paracentric inserted inversion. *Am J Hum Genet* 32:731–735 (1980).
- Youngs S, Ellis K, Ennis S, Barber J, Jacobs P: A study of reciprocal translocations and inversions detected by light microscopy with special reference to origin, segregation, and recurrent abnormalities. *Am J Med Genet A* 126A:46–60 (2004).