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Review article

Inv dup(15) supernumerary marker chromosomes

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In the course of cytogenetic studies, the detection of a supernumerary additional small marker chromosome is not an uncommon occurrence. In lymphocytes the presence of such a marker, once identified, may be directly correlated with the clinical phenotype but in prenatal samples such as CVS or amniocytes there are often difficulties in interpretation. These difficulties not only involve the identification of the chromatin fragment from which the additional material has been derived but also the prediction of its likely effect upon the phenotype.

The first problem is gradually being overcome with the advent of fluorescence in situ hybridisation (FISH) which has the ability to identify chromatin material selectively by using chromosome specific libraries. The difficulty in relating marker to phenotype will only become resolvable by defining not only the original location of the extra material but also how much excess euchromatin is actually present.

One of the most common chromosome markers is the inv dup(15) or idic(15), which may represent as many as 50% of the small supernumerary chromosomes detected during routine karyotyping. Buckton *et al*[1] in their study of 44 marker chromosomes found an inv dup(15) to account for 17 of those detected. In a survey of 16 395 newborn babies they found an incidence of supernumerary markers of 0·24 per 1000. Among 1142 persons with congenital abnormalities, however, the incidence was 10 times higher at 2·63 per 1000. In another study of 5049 newborn babies, 0·06% were found to carry markers, of which 33/64 were inv dup(15).[2]

The phenotype of probands who carry such a marker varies considerably from apparently unaffected persons to those who are severely mentally retarded. Correlations have been attempted between the severity of the phenotype and the size of the additional marker chromosome but the degree of polymorphism associated with proximal chromosome 15 makes accurate estimation of the amount of euchromatin present in the marker very difficult. Robinson *et al*[3] have shown by molecular methods that clinical severity can be related to gene dosage rather than to the actual physical size of the marker chromosome. The majority of inv dup(15) chromosomes reported have two distinct centromeres with an area of euchromatin lying between them, but in many cases one of the centromeres appears to be inactive, giving the dicentric marker the appearance of an acrocentric chromosome.

One interesting aspect of the presence of an additional marker chromosome derived from proximal 15q is its occasional occurrence in conjunction with Prader-Willi syndrome (PWS). Prader-Willi syndrome is generally associated with a loss of material in proximal 15q rather than a gain. Approximately 75% of patients with PWS have a paternally derived deletion in 15q11–q13[4] while the greater majority of the remaining probands have maternal uniparental disomy (UPD) of chromosome 15.[5] Although in these cases there is no actual loss of chromosome 15 material, the maternal copy of the PWS critical region is believed to be imprinted and non-functional.[6] Angelman syndrome has only very rarely been associated with the presence of a supernumerary marker chromosome derived from proximal 15, despite the finding that the majority of cases also have a deletion in 15q11q13.[7] In this syndrome, the deletion occurs on the maternally derived homologue of chromosome 15,[8] and occasionally paternal UPD of the chromosome has also been observed.[9]

A study of published reports indicates that there have been more than 50 published observations of probands with a supernumerary marker chromosome inv dup(15) or idic(15). The clinical phenotype and the reported size of the marker chromosome are so variable that it was decided to investigate the possibility of classifying the marker chromosomes into groups according to their size and appearance and then to correlate this with phenotype. There are several different methods used to indicate the size and type of any particular marker chromosome. Where photographs are published and comparisons made with these descriptions, it appears that despite these variations, the markers can be divided into groups as follows.

Group 1: small inv dup(15) markers. This group includes all those markers with apparently one centromere caused by close proximity of the two pericentromeric regions. It also includes markers with two distinct centro-

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The earliest papers describing a supernumerary inv dup(15) tended to refer to a "marker" or an "SBAC" (small bisatellited acrocentric chromosome) and are included in this review if the marker is distamycin/DAPI positive. In later work, the term "inv dup (15)" predominates, even though at one point "idic (15)" was considered to be more accurate, and is the term favoured by ISCN (1985). Although in the papers quoted either term is encountered, for the sake of clarity and because the later molecular papers all quote "inv dup(15)" this term has been used throughout.

meres but described as being smaller than a G group chromosome and also those classified as belonging to the AI group as delineated by Steinbach *et al.*[10] Still others were described as metacentric, or having breakpoints in 15q11.

Group 2: medium sized inv dup(15) markers. This group all had two distinct centromeres with some visible chromatin between them. They were often also defined as the same size as a G group chromosome or as belonging to type AII in the Steinbach *et al*[10] classification. Often they were referred to as submetacentric or sometimes even acrocentric in type. The breakpoints in these markers tended to lie in 15q12. As one of the two centromeres is usually inactive, this marker chromosome sometimes has the appearance of a small submetacentric chromosome.[11]

Group 3: large inv dup(15) markers. These also have two separate centromeres which may have distinct banding observable between them. The group also includes markers described as being larger than a G group chromosome and those falling into type AIII in the Steinbach *et al*[10] classification. This type of marker was often described as acrocentric or like an acrocentric chromosome, and the breakpoints lie in 15q13 or in a more telomeric band of chromosome 15.

Further classification was needed to describe situations which did not fall simply into one of these three categories. These included familial or inherited markers and the rare occurrence of more than one marker in a single person. In addition, cases of PWS and the chance finding of supernumerary inv dup(15) in the course of prenatal diagnosis were also considered independently, as was the presence of the marker in mosaic form.

Group 1: markers which only contain extra material from pter-q11. Table 1 contains a summary of reports describing group I or small supernumerary inv dup(15). Of the 12 probands recorded, mental retardation or developmental delay was present in only five, while the other seven were stated to be mentally normal. There was a marked absence of other clinical findings in this group. There were four cases of PWS with the clinical signs accompanying this diagnosis but, otherwise only the patient ascertained from a survey of mental hospitals[1] was found to be mentally retarded with dysmorphic features. This type of marker is sometimes fortuitously detected in amniotic fluid or CVS samples, or through population surveys, while two of the probands were detected during surveys of secure institutions.[1]

Group 2: markers containing extra material from pter-q12. Table 2 summarises reports of medium sized supernumerary inv dup(15) chromosomes classified into group 2. Ascertainment in 25/37 cases was a consequence of mental retardation or developmental delay. Other reasons for ascertainment included autism[27] and a case of neuroleptic malignant syndrome.[29] One subject was found in the course of a newborn survey[1] and a further four were detected during prenatal diagnosis.[25 30] Only seven out of 36 persons were mentally normal and some mental handicap was reported as severe or even profound. Many of the probands had behavioural problems or seizures or both and several had an abnormal EEG (table 3). Among the seven subjects who were not described as having mental retardation or developmental delay, two were ascertained through a survey of newborns and a third was the unaffected mother of a girl with Turner's syndrome. This latter marker was however familial and maternally derived (table 3). One further subject with normal intelligence was from a maximum security hospital.[1]

Obesity was not a feature of these probands and neither was hypogonadism, and approximately half of them were without physical stigmata.

Group 3: large inv dup(15) markers containing material from 15pter-q13. Table 4 summarises reports of supernumerary inv dup(15) chromosomes classified into group 3. Ascertainment in almost all cases was by mental retardation or developmental delay.

This third group of inv dup(15) marker chromosomes contains all those described as larger than a G group chromosome. They are often seen as acrocentric rather than dicentric and the breakpoints are at q13:q13 or even in one case q14:q14 (table 4). All probands described were mentally retarded (this being the main reason

Table 1 Reports and clinical summary of probands with a small inv dup(15)

Study	Ascertainment	Sex	Age	Size	Type	Breakpoints	Origin	MR or DD	Mat age	Pat age	Hypotonia	Obesity	Abn EEG	Hypogonadic or infertility	Dysmorphic	Seizure
Ridler *et al*[12]	PWS	F	17 y	<G	Meta			+			+		+			
Fujita *et al*[13]	PWS	F	3 y		idic	q11:q11		+	39	40	+	+				
Wisniewski *et al*[14]	PWS	M	17 y	<G	Meta	q11 or q12	Pat	+	34	36	+	+	No	+		No
Stetton *et al*[15]	Mother/PND	F		<G		q1:q1		No								
Mattei *et al*[16]	PWS, case 9	M	16 mth	<G	Meta	q11:q11		+	29	29	+	No	No	+		No
Wisniewski and Doherty[17]	Father/ PND, case 1	M	36 y	<G		q1:q1		No								
Buckton *et al*[1]	Cancer survey 64/11/69	M	61 y	<G		q1:q1		No	26	28					No	
	Mental hosp 84/69	M	53 y	<G		q1:q1		+	41	47				−	+	
	Max security 113/73	M	20 y	<G		q1:q1		No								
	Prison survey 129/80	M	58 y	<G		q1:q1		No	40	47				No		
Maraschio *et al*[11]	Case 4	M	37 y	<G	Meta	q11.2:q11.2		No	37	38				+		
Callen *et al*[18]	Survey case 1	F			Meta	q1:q1		No								

Abbreviations used in the tables. PWS = Prader-Willi syndrome. MR = mental retardation. DD = developmental delay. Mat = maternal. Pat = paternal. Abn = abnormal. Meta = metacentric. Sub-meta = sub-metacentric. Acro = acrocentric. PND = prenatal diagnosis. Max = maximum. Hyper = hypertonia. IUGR = intrauterine growth retardation. M = marker. DD = distamycin/DAPI. Spont = spontaneous. Fam = familial.

Table 2 Reports of probands with a medium sized inv dup(15)

Study	*Proband*	*Ascertainment*	*Size*	*Type*	*Breakpoints*	*Origin*	*Mat age*	*Pat age*	
De Falco and Willey[19]		Institution	=G	Acrocentric					
		Institution	=G	Acrocentric					
		Institution	=G	Acrocentric					
Chamberlin *et al*[20]		Mental retardation	=G			Mat	30	35	
Maraschio *et al*[21]	Case 1	Developmental delay			q12:q12	Mat	26	28	
	2	Developmental delay			q13:q13	—	44	49	
	3	Developmental delay			q13:q13	Mat	39	43	
	4	Developmental delay			q13:q13	Mat	35	38	
	5	Developmental delay			q13:q13	Mat	26	26	
	6	Developmental delay			q13:q13	Pat	30	35	
	7	Developmental delay			q13:q13	Mat	41	35	
	8	Developmental delay			q13:q13	Mat	42	44	
Yip *et al*[22]	Case 2	Institution	=G	Metacentric					
Gilmore *et al*[23]		Developmental delay	=G		q12		30	44	
Buckton *et al*[1]	245/66	Parent of Turner	=G		q1:q1	Fam/Mat	21	44	
	76/69	Mental hospital survey	=G		q1:q1		27	30	
	78/69	Mental hospital survey	=G		q1:q1		—	—	
	163/72	Coeliac disease	=G		q1:q1		34	41	
	227/76	Newborn survey	=G		q1:q1		27	26	
	251/78	Max security survey	=G		q1:q1		31	—	
	JC	Mental retardation	=G		q1:q1		31	35	
Wisniewski and Doherty[17]	Case 3	Developmental delay	=G						
Mohandas *et al*[24]	Case 1	Developmental delay	=G		q1:q1		32		
Miny *et al*[25]		Prenatal diagnosis	=G	Submeta	q12:q12		36	37	
Kirklionis and Sergovich[26]		Institution survey			q12:q12				
		Institution survey			q12:q12				
		Institution survey			q12:q12				
Wahlstrom *et al*[27]		Autism	=G						
Nicholls *et al*[28]	HS38	Developmental delay		Submeta	q11:q13 or q12:q12				
Lazarus *et al*[29]		Neuroleptic malignant syndrome	=G						
Plattner *et al*[30]	Case 3a	Amniotic fluid		AII					
	Case 4a	Amniotic fluid		AII					
	Case 5a	Amniotic fluid		AII					
Callen *et al*[18]	Case 5	Anxiety		Submeta					
Rauch *et al*[31]	Case 2	Tetralogy of Fallot	=2×18p				27	32	
Robinson *et al*[3]	Case B	Developmental delay		Submeta	q11:q13	Mat	32	35	Heteromorphic
Plattner *et al*[32]	Case 13	Developmental delay			q12	Mat	31		

Table 3 Clinical findings in probands with medium sized inv dup(15)

Study	*Proband*	*Sex*	*Age*	*Hypotonia*	*Abnormal EEG*	*Short stature*	*Hypogonadism or infertility*	*Behavioural problems*	*Autism*	*Dysmorphic*	*Seizures*	*MR or DD*	*Physically normal*
De Falco		M										+	+
and Willey[19]		M										+	+
		M										+	+
Chamberlin *et al*[20]		F	12 y			+	No			+		Profound	
Maraschio *et al*[21]		M	6 y	Hyper	+	−		+			+	+	
		F	12 y	Hyper	+	+		+			+	+	
		M	21 mth	+	+	−	+	+			−	+	
		M	10 y	−	+	−		+			+	+	
		M	5 y	+	−	−		+		+	−	+	
		F	8 mth	+	−	−		+			+	+	
		F	4 y	−	+	+		+			−	+	
		F	15 y	+	−	−	No	−			−	+	
Yip *et al*[22]		M	46 y			No				No		Severe	+
Gilmore *et al*[23]		M	2½ y	No	−	No		+		No		Moderate	+
Buckton *et al*[1]	245/66	F	50 y				−			No		No	+
	76/69	F	25 y				+			+	+	+	No
	78/69	F	15 y				No			No	+	+	No
	163/72	M	65 y				No			No		No	+
	227/76	M	0 y				−			−		No	+
	251/78	M	24 y				−			−		No	
	JC	F	22 y				−			+	+	Severe	No
Wisniewski and Doherty[17]	Case 3	M	20 mth	No		+	+			+	No	+	
Mohandas *et al*[24]		M	3 y	Hyper	+			+			+	+	
Miny *et al*[25]		M		+	+			+	+		+	Severe	
Kirklionis and		M	Adult	+			+	+			+	+	
Sergovich[26]		M	Adult	+			+	+			+	+	
		M	Adult	+			+	+			+	+	
Wahlstrom *et al*[27]		M	32 y						+				Not D/D +ve
Nicholls *et al*[28]		F	2 y	+	+	No				+		Moderate	
Lazarus *et al*[29]		M						+		+		Severe	
Plattner *et al*[30]		F	Adult									No	
		F	Adult									No	
		F	Adult									Slow	
Callen *et al*[18]		M										No	
Rauch *et al*[31]		M	2·4 y							+		+	
Robinson *et al*[3]		M	13 y			No		+				Moderate	
Plattner *et al*[32]		F	16 mth	+		No				+		+	

for referral while others were ascertained through surveys of mental institutions). Although most of the subjects in this group had severe or profound mental handicap, Shreck *et al*[33] found three of six subjects to be only mildly affected although all six had markers of approximately the same size. Besides a degree of mental handicap ranging from mild to profound, other problems encountered in this group of subjects included seizures, hypotonia, behavioural problems, which occasionally included autism, and dysmorphic features. A large number of probands also had an abnormal EEG. This group was most closely represented by those features associated with "inverted duplication 15 syndrome" (tables 5 and 6).

Table 4 Reports of probands with a large sized inv dup(15)

Study	Proband	Ascertainment	Size	Type	Breakpoints	Origin	Mat age	Pat age	
Shreck *et al*[33]	JF		>G	Acro			39	33	
	CS		>G	Acro			42	45	
	GK		>G	Acro			36	42	
	JT		>G	Acro			34	53	
	LV		>G	Acro			—	—	
	RD		>G	Acro			—	—	
Wisniewski *et al*[34]	Case 1		>G		q1:q1	—	30	26	
	2		>G		q1:q1	Mat	36	38	
	3		>G		q1:q1	Mat	38	38	
	4		>G		q1:q1	—	34	34	
	5		>G		q1:q1	—	35	40	
Zanotti *et al*[35]	Case 1	Developmental delay			q21 or q22		30	33	Heteromorphic
	2	Developmental delay			q21 or q22		36	48	Heteromorphic
	3	Developmental delay			q21 or q22		28	32	Heteromorphic
	4	Developmental delay			q21 or q22		29	40	Heteromorphic
	5	Developmental delay			q21 or q22		26	28	
Yip *et al*[22]	Case 1	Developmental delay	>G	Submeta			37	28	
Buckton *et al*[1]	99/75	Mental hospital survey	>G				27	25	
	180/77	Mental hospital survey	>G				25		
Schmid *et al*[36]		Developmental delay	>G			Mat	29		
Hoo[37]		Developmental delay	>G	Acro	q13:q13	Mat	32	31	
Maraschio *et al*[11]	Case 2	Psychomotor retardation	>G	Acro	q12:q12	Mat	40	44	
Nicholls *et al*[28]	HS15	Mental retardation			q13	Mat			
Plattner *et al*[30]	Case 6	Developmental delay	AIII		q13	Mat	29		
Shibuya *et al*[38]		Developmental delay			q14:q14	Mat	30	31	
Callen *et al*[18]	Case 7	Mental retardation		Acrocentric					
Robinson *et al*[3]	Case A	Developmental delay			q13:q13	Mat	28	34	
	Case D	Seizures			q13:q13	Mat	31	31	
	Case E	Developmental delay			q13:q13	Mat	32	30	

Table 5 Clinical findings in large sized inv dup(15)

Study	Sex	Age	Hypotonia	Obesity	Abnormal EEG	Short stature	Hypogonadism or infertility	Behavioural problems	Autism	Dysmorphic	Seizures	MR or DD
Shreck *et al*[33]	JF M		−				−	−	+	−	−	Moderate
	CS M		+				+	−		+	+	Profound
	GK M							−				Profound
	JT F							+				Mild
	LV F			No		No		+		No		Mild
	RD M			No		No		+		No		Mild
Wisniewski *et al*[34]	F		+		+	+	No	+			+	+
	M		+		+	−	−	+			+	+
	M		+		+	−	−	+			+	+
	F		+		+	−	No	+			+	+
	F		−		−	+	No	+			−	+
Zanotti *et al*[35]	M	22	Hyper	No	+	+		+		No	+	Severe
	M	7	+		+			+		No	+	Severe
	F	6	−		+			+		+	−	Severe
	M	16 mth	+		+			−		+	+	Severe
	F	3 mth	+		No			−		No	−	Severe
Yip *et al*[22]	M	4		No		+				+		Severe
Buckton *et al*[1]	M	6					+			+	+	+
	F	11					No			+	+	+
Schmid *et al*[36]	F	2		No		+				+		Mild–moderate
Hoo[37]	M	4								No		Mild–moderate
Maraschio *et al*[11]	M	3 y										
		7 mth	−							+		Severe
	M	4 y										
		10 mth	+									+
Nicholls *et al*[28]	F HS15		+					+	+			Moderate
Plattner *et al*[30]	M, case 6	2·5		No		+				+		+
Shibuya *et al*[38]	M	15		No	+						+	+
Callen *et al*[18]	M							+	−	+	−	Severe
Robinson *et al*[3]	M		+	+	+	+	+	−			+	Severe
	M		−	−	+	+		+			+	Severe
	M		+	No	+	+		−			+	Severe
Towner *et al*[39]	M	10	−				+	+		+	+	+
	M	2	+				−	−		+	−	+
	F	Adult	−				−	−		−	−	+
	M	5	+				−	+		+		+

Table 6 Summary of clinical findings in inv dup(15) probands

	Total	M	F	Mat age	Pat age	MR/ DD	Hypotonia	Abnormal EEG	Short stature	Hypogonadism	Behavioural problems	Dysmorphic	Seizures
Group 1	12	8	4	35·1	37·9	5/12	4/12	2/12	—	3/12	—	1/12	0/12
Group 2	37	23	14	32·1	36·5	29/36	10/37	8/37	3/37	6/37	15/37	9/37	12/37
Group 3	34	23	11	32·5	35·6	34/34	14/34	12/34	9/34	4/34	16/34	12/34	15/34
Mosaic markers	15	7	8	36·5	41·8	9/15	3/15	2/15	4/15	3/15	2/15	3/15	2/15

Multiple copies of inv dup(15)

Multiple copies of an inv dup(15) have been reported with very variable effects (tables 7 and 8). Three infertile males have been found to have more than one copy of such a marker with apparently no mental impairment.[42–44] In all three cases, however, the supernumerary markers were of group 1 size, and were described as either metacentric or smaller than a G group chromosome. In two of them the marker was familial, once paternally inherited and once maternally inherited. Each of the parents, however, only carried a single copy.

In another subject the two markers detected were quite distinct from one another, one being from group 1 and the other from group 3.[40] Despite neither being present in all of the mitoses studied, the proband was severely mentally handicapped, as was a female described by Robinson *et al.*[3] In this latter case, the two markers were alike and neither was present in mosaic form. Although this case was ascertained prenatally, the pregnancy went to term. A second similar case, described by Wisniewski *et al*[17] in 1985, had two markers present in 79 to 95% of cells but this pregnancy was terminated.

Mosaicism involving inv dup(15) (tables 9 and 10)

The presence of a supernumerary inv dup(15) marker chromosome in only a percentage of mitoses might be expected to alleviate the severity of the clinical phenotype. However, the relationship between marker size and effect on phenotype makes any relationship difficult to define. Four cases of mosaicism have been found in persons with a diagnosis of PWS, but all four markers were from group 1, being smaller than a G group chromosome in size, exactly as for the other cases of PWS.[45–47] There were five persons with mosaic inv dup(15) without developmental delay or mental retardation,[1 18 32 41] but of these three had small group 1 sized markers. Two of the three were ascertained from surveys, one of cancer patients and

Table 7 Reports of multiple inv dup(15)

Study	*Proband*	*Ascertainment*	*Size*	*Type*	*Breakpoints*	*Origin*	*Mat age*	*Pat age*	
Van Dyke *et al*[40]		Mental retardation	M1 > G M2 < G	Acrocentric Metacentric			38		52% of cells M1 20% of cells M1 + M2
Voss *et al*[41]		Developmental delay		Metacentric Acrocentric	M1 M2q15		27	29	No mosaicism. Father has M1
Wisniewski and Doherty[17]	Case 2	Prenatal diagnosis			M1q13:q13 M2q13:q13		38	27	79–95% of cells. Terminated
Martin-Lucas *et al*[42]		Infertility	M1 < G M2 < G	Submetacentric Submetacentric	q11.2:q11.2 q11.2:q11.2		43	49	No mosaicism, one C band
Masnenti[43]		Infertility			M1q11:q11 M2q11:q11	Mat	45		Heteromorphic Familial
Gentile *et al*[44]	Case 2	Infertility	M1 < G M2 < G	Metacentric Metacentric		Pat	31	33	Two C bands Familial
Robinson *et al*[3]	Case C	IUGR			M1q13:q13 M2q13:q13	Mat	33	39	No mosaicism

Table 8 Clinical findings in multiple inv dup(15)

Study	*Sex*	*Age*	*Hypotonia*	*Obesity*	*Abnormal EEG*	*Short stature*	*Hypogonadism or infertility*	*Behavioural problems*	*Autism*	*Dysmorphic*	*Seizures*	*MR or DD*
Van Dyke *et al*[40]	M	7			+			+		No		Severe
Voss *et al*[41]	M	16		No	+	+	No			+	+	Severe
Martin-Lucas *et al*[42]	M	36					+					No
Manenti[43]	M	27					+					No
Gentile *et al*[44]	F	32				No	+	No	No	No		No
Robinson *et al*[3]	F	7	+	No		+					+	Severe

Table 9 Reports of probands with mosaic inv dup(15)

Study	*Proband*	*Ascertainment*	*Size*	*Type*	*Mat age*	*Pat age*	*% mosaicism*	
Van Dyke *et al*[40]		Mental retardation	M1 > G M2 < G	Acrocentric Metacentric	38		52% 1Mar 20% 2Mar	
Michaelson *et al*[45]		PWS	< G	Acentric	35	40	30/40	No D/D
		PWS	< G	Acentric	43	49	8/15	No D/D
Voss *et al*[41]		Father of affected boy	< G	Metacentric			70%	
Ledbetter *et al*[46]		PWS	q11:q11	Metacentric			16/20	
Goh *et al*[47]		PWS	< G	Metacentric	37	44	60%	May not be 15
Buckton *et al*[1]	293/67	Mental def survey	> G		35	34	80%	
	90/70	Cancer survey	< G		43	43	27%	
	21/72	Subfertility	< G		39		40%	
	65/78	Mental hosp survey	> G		35		81%	
Mohandas *et al*[24]	Case 2	Developmental delay	= G		32		21/50	
Maraschio *et al*[11]	Case 1	Psychomotor retardation	> G q12:q12	Acrocentric	36	41	92%	Mat derived
Plattner *et al*[30]	Case 7	Prenatal diagnosis	AII		36		9/15	
Callen *et al*[18]	Case 6	Developmental delay		Acrocentric				
	Mother of case 8	Mother of affected girl		Acrocentric/ Dicentric				
Plattner *et al*[32]	Case 12	Features of Down's syndrome	q12		29		68%	Mat derived

the other of subfertility,[1] whereas the third was the phenotypically normal father of an affected child.[41] Father and son both had a large metacentric marker, but although the phenotypically normal father had this marker in 70% of his cells, his severely handicapped son had the same marker and also an additional morphologically distinct inv dup(15) marker in all mitoses studied.

In the case described by Callen *et al*[18] in 1992 the phenotypically normal mother of a retarded child carried a marker equal in size to a G group chromosome. The marker was present in only a proportion of maternal cells but the percentage was not given.

Disregarding the size of the supernumerary marker chromosome, the persons who remained unaffected or were only mildly affected had between 27% and 70% of mitoses with a marker, and an average of 53%. Those more severely affected had between 52% and 82% with an average of 74%.

Marker inv dup(15) chromosomes ascertained at prenatal diagnosis

A supernumerary inv dup(15) marker has been estimated to occur in approximately 1 in 6000 prenatal diagnoses.[36] In six studies describing the fortuitous detection of such markers in the course of prenatal diagnostic studies, 11 of 12 were ascertained in amniotic fluid and one in CVS. The outcomes of the 12 pregnancies reflect the dilemmas presented to the parents (table 11). Six of the pregnancies were terminated despite the fact that three of the markers were familial. Of the six which continued, two markers were also familial, but in neither case was the outcome described, and a third baby with a de novo "G like" inv dup(15) marker was severely retarded.[25] The final three were apparently normal, but of these one also inherited the marker from the mother and in a second it was present only in mosaic form.[30] This latter baby was developmentally normal at $2\frac{1}{2}$ years of age[32] but it would be interesting to learn of the later development of the other four babies (table 11).

Familial inv dup(15) markers in persons other than subjects of prenatal diagnoses

With few exceptions, the markers found to be segregating within families were of group 1 size, described as either metacentric or smaller than a G group chromosome, and none was large enough to be included in group 3. In one, the proband was ascertained through failure to thrive.[49] Although this marker was equal in size to a G group chromosome, it was present in mosaic form in both a father and his daughter, neither of whom were mentally retarded. In two families, infertile males inherited an inv dup(15), but in the parents only single markers were present whereas the probands were found to have two[43,44] (table 7). Other familial cases were ascertained either because the persons who carried the supernumerary chromosome were the parents of children who also carried them and so were not themselves the probands, or they were ascertained in the course of population surveys. Out of a total of 14 persons described in table 12 who had inherited the inv dup(15) marker from a normal parent, 11 were unaffected and two were described as "slow" or with mild handicap. One child with developmental delay and autistic features had inherited the marker from her mother who carried it in mosaic form.[18] There were three cases where a handicapped mother passed on an inv dup(15) to her handicapped child. A large marker

Table 10 Clinical findings in mosaic inv dup(15)

Study	Sex	Age	Hypotonia	Obesity	Abnormal EEG	Short stature	Hypogonadism or infertility	Behavioural problems	Autism	Dysmorphic	Seizures	MR or DD	Physically normal
Van Dyke *et al*[40]	M	7			+			+		No		Severe	
Michaelson	M	2 y 8 mth	+	+	No	+	+					+	
et al[45]	M	8 y	+	+		+	+					Mild	
Voss *et al*[41]	M	45										No	
Goh *et al*[47]	F	35	+	+		+						IQ 64	No
Buckton *et al*[1]	F	31		−			No			+	+	+	No
	F	69		−			−			No	−	No	+
	F	27		−			+			No	−	No	+
	F	39		+			−			No	−	IQ 44	+
Maraschio *et al*[11]	M	5	−	−	−	−	−	−		+		IQ 79	No
Mohandas *et al*[24]	M	4 mth			+						+	+	
Plattner *et al*[30]	F	Prenatal										No	+
Callen *et al*[18]	M							+				Mild	
	F											No	
Plattner *et al*[32]	F	1·5 mth	+	No		+				+		No	

Table 11 Reports of inv dup(15) detected at prenatal diagnosis

Study	Proband	Ascertainment	Size	Type	Breakpoints	Origin	Mat age	Pat age	Mosaic	Outcome	
Stetten *et al*[15]	Case 1	Amniotic fluid	<G		q1:q1	Mat	36	37	No	Terminated	Familial
Wisniewski and	Case 1	Amniotic fluid			q13:q13	Pat			No	Terminated	Familial
Doherty[17]	Case 2	Amniotic fluid			q13:q13		38	27	75–95%	Terminated	2 copies
Mohandas *et al*[24]	Case 3	Amniotic fluid	=G		q1:q1		29		No	Terminated	
Miny *et al*[25]		Amniotic fluid	=G	Submetacentric	q12:q12				No	Severe MR	
Maraschio *et al*[11]	Case 6	Amniotic fluid	<G	Metacentric	q11:q11	Pat	41		No	Terminated	Familial
Plattner *et al*[30]	Case 1	Amniotic fluid	AI				39		No	Terminated	
	Case 2	Amntiotic fluid	AIII				39		No	Normal at 3 months of age	
	Case 3	Amniotic fluid	AII			Mat	39		No	Continued	Familial
	Case 4	Amniotic fluid	AII			Mat	41		No	Continued	Familial
	Case 5	CVS	AII			Mat	44		No	Normal at birth	Familial
	Case 7	Amniotic fluid	AII				36		17/22	Normal at $2\frac{1}{2}$ years[32]	

Table 12 Reports of familial inv dup(15)

Study	*Proband*	*Ascertainment*	*Size*	*Type*	*Breakpoints*	*Origin*	*Mat age*	*Pat age*	*MR or DD*	
Stetten *et al*[15]	Case 1a	Prenatal diagnosis	<G		q1:q1	Mat			No	Heteromorphic
Knight *et al*[48]	Case 1	Failure to thrive	=G		q12:q12	Pat			No	61% 1 marker
	Case 1a	Father	=G			Mat	24	25	No	22% 2 markers
Wisniewski *et al*[17]	Case 1	Prenatal diagnosis	<G		q1:q1	Pat	36	33		Terminated
		Father							No	
Buckton *et al*[1]	245/66	Child with Turner	=G			Mat	21	30	No	
	11/69	Cancer	<G				26	28	No	
Maraschio *et al*[11]	Case 3	Psychomotor retardation	>G	Acro	q12:q12	Mat	37	38	+	
		Mother of case 3							+	
	Case 5	Two spont abortions	=G	Submeta	q11.2:q11.2	Mat			No	
Plattner *et al*[30]	Case 3a	Amniotic fluid	AII				39		No	
	Mother									
	Case 4a	Amniotic fluid	AII				41		No	
	Mother									
	Case 5a	CVS	AII				44		Slow	
	Mother									
Callen *et al*[8]	Case 2	Prenatal diagnosis		Meta					No	
		Mother of case 2							No	
	Case 3	Developmental delay		Meta					Mild	
		Mother of case 3								
	Case 4	Parental anxiety		Submeta					No	
		Mother of case 4							No	
	Case 8	Developmental delay		Acro/		Mat			+	
		Mother of case 8		dicentric					No	Mosaic
Towner *et al*[39]	Case 1	Developmental delay			q13	Mat			+	
	Case 2	Developmental delay			q13	Mat			+	
	Mother								+	

Table 13 Inv dup(15) in Prader-Willi syndrome

Study	*Ascertainment*	*Size*	*Type*	*Breakpoints*	*Mosaic*	*Origin*	*Mat age*	*Pat age*	
Ridler *et al*[12]	PWS	<G	Metacentric		No				
Michaelson *et al*[45]	PWS	<G	Acentric		30/40		35	40	Not 15?
	PWS	<G	Acentric		8/15		43	49	No D/D
Wisniewski *et al*[14]	PWS	<G	Metacentric	q11 or 12	No	Pat	34	36	Paternal heteromorphic
		<G	Metacentric						
Fujita *et al*[13]	PWS		idic	q11:q11			39	40	
Ledbetter *et al*[46]	PWS		idic	q11:q11	16/20				
Mattei *et al*[16]	PWS		Metacentric	q11:q11	No		29	29	
	Case 9								
Goh *et al*[47]	PWS	<G	Metacentric		60%		37	44	

Table 14 Complex translocations

Study	*Ascertainment*	*Karyotype*
Wulfsberg *et al*[49]	PWS	40% 46,XX, 60% (15:1)(p11) translocation 40% of the translocation cells +isodic (15p)(q11)
Kousseff *et al*[50]	PWS	45,X t(Y:15) with del 15pter–15q12 47,X t(Y:15) dic(15) dic(15) q12:q12
Murdock and Wurster-Hill[51]	PWS(?) Profound MR	46,XY,–5–15 +der(5) t(5:15) 5pter–5q35::15q13–15ter) +idic(15)(pter–q13::q13–pter)
Kousseff *et al*[52]	PWS	Small marker resulting in trisomy 46,XY,/47,XY, +del (15)(pter–q13) Trisomy marker
Voss *et al*[41]	Severe psychomotor retardation	48,XY, +15q– +marker 15
Narahara *et al*[53]	PWS	47,XX, del(15)(q11.200:q11.207), +idic(15)(pter–q11.1::q11.1-pter)

passed from a moderately retarded mother to two sons with developmental delay has recently been described by Towner *et al*,[39] and Maraschio *et al*[11] described a child with psychomotor retardation who had inherited an inv dup(15) from his mentally handicapped mother.

Derivation of the marker chromosome

Of 13 reported cases of familial inv dup(15), 11 were maternally and two paternally inherited. In probands who carried a de novo marker, by far the greater majority were maternally derived. The origin of only one of the small metacentric markers was ascertained. It was associated with Prader-Willi syndrome and was paternal in derivation.[14] Of the second, G sized group of markers, when they occurred de novo, nine were maternally and only one was paternally derived and where the marker was larger than a G group chromosome in size, all 11 were maternally derived.

Prader-Willi syndrome

Eight cases of supernumerary inv dup(15) which have been described in conjunction with Prader-Willi syndrome are described in table 13. All eight markers are from group 1 and four of eight are present as mosaics. Interestingly in the single case where parental origin was ascertained, the marker was paternally derived.[14]

Complex karyotypes

Six cases of a complex karyotype which involved an inv dup(15) chromosome are described in table 14. Although five of six had a diagnosis of possible Prader-Willi syndrome, most of the translocations were of a sufficient complexity that the involvement of other chromosomes may be equally responsible for the phenotypic expression.

Conclusions

The effect exerted upon the phenotype of a supernumerary inv dup(15) marker chromo-

some, although apparently directly related to its size, may in reality depend upon the number of specific active genes present within the karyotype.[3] This will obviously bear a superficial relationship to marker number and size but is complicated by two factors, firstly the large polymorphic variation between subjects in the region of proximal 15q and secondly the actual breakpoints present in the marker. A person with a 15q11:q13 breakpoint may be more severely affected than one with 15q12:15q12 breakpoints although the markers may be indistinguishable in size.

All of the chromosomes reported with the exception of some familial cases were maternally derived. This implies either that this type of marker is very rarely formed during male gametogenesis or that an inv dup(15)(pat) is lethal. Even those markers associated with PWS tend to be maternally derived, a fact which may reflect the fine balance of active genes, as the maternal copy of the PWS region is believed to be imprinted and non-functional. If this is so, then a 1:1 ratio of genes should be the same as a 1:3 ratio. This may be analogous to X inactivation in Turner's syndrome where, despite the pseudoautosomal region, a 1:1 ratio of active:inactive X linked genes does not exert the same phenotypic effect as a 1:0 ratio of X linked genes. Possibly the increase in severity of phenotype with size is related to the inclusion of regions where the maternal copy is functional as such markers may include the AS region and beyond, where the maternal copy of proximal 15 carries active genes.

Recently, two cases of inv dup(15) were described in association with PWS and AS respectively.[54] Both marker chromosomes were small, of the type which had previously been associated with PWS, having breakpoints at q11:q11 in the proband with AS and possibly q12:q12 or q11:q12 in the boy with PWS. Molecular studies showed that in both cases the likely cause of the phenotype was not the presence of an inv dup(15) but uniparental disomy (UPD). If, as these authors suggest, the presence of an inv dup(15) can be associated with or predispose to uniparental disomy, then evaluation by molecular methods of the other cases of PWS with a small inv dup(15) marker may also show UPD. If this proves to be the case, then the association between PWS and a small chromosome 15 supernumerary marker may not be the result of a direct relationship between copy number and clinical outcome but merely reflect an increased predisposition to maternal UPD. Further molecular studies should be used in cases of inv dup(15) to establish both the relationship between smaller markers, PWS, and UPD and to investigate gene dosage, marker size, and clinical manifestation further.

The first case of a fortuitous detection of a de novo inv dup(15) occurred in an amniotic fluid sample from a proband referred for increased maternal age. Despite the inv dup(15) having breakpoints in q12:q12, being as large as a G group chromosome and de novo, the pregnancy continued to term. At 16 months, the child had severe mental and motor retardation.[25] In other cases where the marker was both small and metacentric, no phenotypic effect was exerted, but still others resulted in a termination of pregnancy even when the marker had been familially inherited, reflecting the uncertainty associated with prenatal marker detection. It would seem that despite the relationship between marker size and phenotype, the finding of a marker prenatally causes diagnostic dilemmas.

Buckton *et al*[1] described 17 patients with inv dup(15), relating the size of the marker to a G group chromosome. They found that if the marker was larger than a G group chromosome even in mosaic form, the proband was mentally retarded. Of seven probands with a marker of G group size, none was mosaic, three were mentally retarded, and four were of average intelligence. In contrast, however, if the marker was smaller than a G group chromosome, even in non-mosaic form, all probands were unaffected.

Molecular studies have been performed in six documented cases. In one of these studies a single patient with MR and intractable epilepsy was shown to be tetrasomic for D15S9.[38] This locus lies within the PWSCR indicating that at least part, and from the karyotype breakpoints given (q14:q14) probably all, of the PWSCR and ASCR were present in four copies. The other five patients were all investigated by Robinson *et al*[3] who found a supernumerary marker to be present in a variety of combinations. If the markers were of group 2 size with a duplicated region including CMW-1 (D15S24), and therefore covering all of the PWS/AS critical region, the probands all had severe mental and motor retardation with seizures. Moderate retardation and aggressive behaviour were associated with a smaller marker (patient B), but in a case where the smaller marker was present in two copies, giving six overall at some loci, then the phenotype was once more that of severe mental and motor retardation and seizures with growth retardation (patient C). These findings led Robinson *et al*[3] to suggest that the number of extra copies of the 15q11q13 region may determine the phenotype rather than the size of the marker itself. It will be interesting to compare further molecular studies in order to determine both the effect of marker size and number on the clinical outcome in cases of inv dup(15) marker chromosome.

Isomorphism or heteromorphism in inv dup(15) markers

The determination of whether the inv dup(15) marker was derived from two copies of the same parental chromosome 15 (isomorphic) or from the proximal regions of both parental homologues (heteromorphic) has been made in several cases, particularly for the larger markers. In a single case from group 1, the marker was found to be heteromorphic, whereas in group 2 there were 10 heteromorphic but only two isomorphic markers reported. This pattern was repeated in group 3, where once again there were 10 heteromorphic and two isomorphic markers reported. Buckton *et*

al[1] found 10/12 were heteromorphic and two isomorphic.

A study of 26 cases of inv dup(15) using fluorescence in situ hybridisation (FISH) to determine copy number divided the markers into two types, those with two copies of the PWS/AS critical region and those with none.[55] A significant association was found between the presence of the PWS/AS region and mental retardation. The larger inv dup(15) markers did not fall into a single category, however, as 10/13 had breakpoints proximal to D15S24 while the other three had breakpoints which were distal to this locus. As D15S24 lies in 15q13, this again divides the inv dup(15) into three groups, dependent upon size. It remains to be determined whether the breakpoints in the group 2, medium sized markers are (1) all at the same point and (2) correspond to the more distal of the hot spots described by Kuwano *et al.*[56] The breakpoints for the smaller, group 1 markers may lie at the proximal hot spot described by these authors.[56]

Table 6 summarises the clinical findings shown by probands from the different groups. There is a gradual increase in severity with increasing marker size although there is a greater similarity observed between groups 2 and 3 than between groups 1 and 2, as would be expected. The clinical phenotype shown by probands with mosaicism resembles the milder expression found in group 1. The greatest differences between groups are in the presence of mental handicap where a fifth of probands in group 2 are unaffected, but all of those in group 3 showed delay, and in stature where more than twice as many probands from group 3 than from group 2 are growth retarded.

Even in cases of familial inheritance of an inv dup(15) marker chromosome, there is a far greater preponderance of maternally inherited (11 cases) than of paternally inherited (two cases), although in the paper by Maraschio *et al*[11] the mother of case 5 had inherited the familial inv dup(15) from her father, making three in all. Even where the marker was detected prenatally, of six familial cases only two were paternally inherited. As both of these were terminated, the effect of imprinting upon a directly inherited inv dup(15) marker has yet to be determined.

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