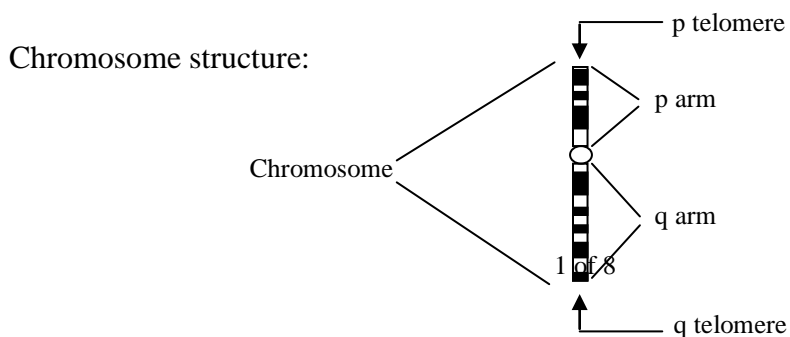


## CHROMOSOME 9 DELETION STUDIES

Over the past decade, 135 chromosomal changes involving chromosome 9 have been studied in our laboratory. All of these have been studied in the laboratory with very detailed studies to determine the precise changes. This is a summary of some of our research on chromosome 9 deletions. It is important to remember that each individual with a chromosome 9 deletion is different and to follow-up with your doctors to make sure your child is receiving the appropriate medical care and services for his or her specific needs.

In order to better understand the findings from our research, it may be helpful to review some basic genetic concepts. Our bodies are made up of billions of cells. Within these cells are structures called chromosomes. Chromosomes contain genes which are the instructions for how we grow and develop, as well as our other inherited features (such as hair and eye color). Typically, there are 46 total chromosomes arranged in 23 different pairs. The chromosome pairs are numbered 1-22, and the remaining pair is known as the sex chromosomes and determines an individual's gender. Each chromosome is divided into a short arm, the p arm, and a long arm, the q arm. The telomeres are the ends of the chromosomes. Please refer to the figure below.



It is important that we have the correct amount of genetic material in order to grow and develop normally. Too much or too little genetic material can cause medical problems, developmental delay, and mental retardation. Individuals with 9p- are missing some amount of genetic material (deletion) on the p arm of one of their copies of chromosome 9.

Our research has shown that these deletions are more complicated than initially suspected. Routine testing does not have the ability to determine the type of chromosome deletion in many cases or exactly how much genetic material is missing. Our research tries to determine this information in order to understand more about the medical and developmental features that 9p- causes.

Of the 135 subjects with changes involving chromosome 9p studied within the laboratory, 63 were included in our recent study to understand the physical characteristics and medical concerns of 9p deletions. All of these subjects: 1) had a clinical assessment by a Medical Geneticist; 2) had provided medical records; 3) had a loss of some chromosome 9 material with no other chromosome changes; and 4) had provided our laboratory with a blood sample so that we could very precisely determine the size of the deletion. Based on these studies the 63 subjects were placed into one of three groups:

1. Large deletions - [44 subjects]
2. Middle sized deletions - [14 subjects]
3. Small deletions - [5 subjects]

There are many features that seem to occur within all three groups, but other findings were clearly different among the groups.

#### Large Deletions:

Trigonocephaly is a hallmark of the 9p deletion syndrome. Trigonocephaly is caused by early closure of one of the sutures (joints in the bones in the skull) which causes an abnormal skull shape. Most of the individuals with large deletions have trigonocephaly and specific typical facial features. These include: upslanting eyes, wide flat nasal bridge, upturned nose, long upper lip, and short neck. The frequency and distribution of these different findings vary among the subjects in our series, but they were clearly much more frequent in the subjects with large deletions. A number of other features were identified in subjects, regardless of the size of the deletion, but were more frequent in the subjects with a large deletion. These included skeletal abnormalities (e.g. long mid fingers, narrow feet, hip dislocations and contractures (loss of joint motion; joint cannot bend)). Other findings seen more frequently in individuals with large deletions include heart defects (and heart murmurs), problems with the immune system/fighting infections, and seizures. Of those who had formal IQ testing and have a large deletion, 46% of the subjects demonstrated mild mental retardation, 49% had moderate mental retardation and 5% had severe mental retardation.

#### Medium and small deletions:

Trigonocephaly was essentially not seen in the individuals with medium and small deletions. Over half of the subjects with medium deletions and only 1 with a small deletion showed some mild cranial abnormalities, such as a prominent forehead. Facial changes were seen less frequently in individuals with medium deletions and almost never

seen in individual with small deletions. Skeletal abnormalities are rarely seen with small deletions and infrequently with medium deletions. Few birth defects were seen with either the small deletions or the medium deletions. Both heart murmurs and heart defects were seen with medium deletions, but not with small deletions. Infections were reported frequently with both the medium and small deletions. While all of the individuals with small deletions showed developmental delay, of those who had formal IQ testing, 80% demonstrated mild mental retardation and only 20% had moderate mental retardation. In the medium deletion group of those who had formal IQ testing, 75% demonstrated mild mental retardation and 25% had moderate mental retardation.

Clearly individuals with medium and small deletions were different than the subjects in the large deletion group in that only 1 of the subjects in the medium and small deletion groups had a suggestion of trigonencephaly. It was difficult to determine if subjects in the medium and small deletion groups should be grouped together or if in fact it is useful to distinguish them as two distinct sets of individuals.

Comparison of Clinical Findings:

Many of the features seen and the difference between groups have been illustrated in Table 1.

**TABLE 1: CLINICAL FEATURES**

Trait	Large Deletions	Medium Deletions	Small Deletions
<b>Size of the Deletion</b>	<b>14.0-19.6 Mb*</b>	<b>9.35-14.0 Mb*</b>	<b>2-7.4 Mb*</b>
<b>Number of Subjects</b>	44	14	5
<b>Craniofacial Abnormalities:</b>			
Trigonocephaly	90%	7.1%	0%
Flat Occiput (back of the head)	28.8%	21.4%	0%
Prominent forehead	26.7%	42.8%	20%
Midfacial Hypoplasia (underdevelopment)	53.3%	57.1%	20%
Eye Abnormalities	82.2%	50%	40%
Strabismus (eyes look in different directions)/Nystagmus (involuntary eye movement)	40%	14.3%	0%
Abnormal Ears	84.4%	57.1%	0%
Abnormal Nose	64.4%	42.4%	20%
Philtrum (above upper lip) Abnormalities	53.3%	64.2%	0%
Abnormal Mouth	75.6%	42.5%	40%
Palate (roof of the mouth) Abnormalities	62.2%	14.3%	0%
Neck Abnormalities	33.3%	7.1%	0%
<b>Skeletal Abnormalities:</b>			
Long middle phalanges (bones of the fingers/toes)	40%	7.1%	20%
Narrow feet	37.8%	21.4%	0%
Hip dislocations	22%	0%	0%
Contractures (loss of joint motion)	44%	0%	0%
<b>Birth Defects:</b>			
Pectus excavatum (sunken chest)	35.6%	0%	0%
Scoliosis/Kyphosis (spine curvature)	31.1%	7.1%	20%
Hernias	62.2%	14.2%	20%
Omphalocele (herniation of intestine/abdominal organs)	4.4%	0%	0%
Cardiac Defects	40%	14.2%	0%
Pyloric Stenosis (narrowed opening of stomach to intestines)	6.7%	0%	0%
GE Reflux (frequent regurgitation/spitting up)	15.6%	0%	0%
Kidney Abnormalities	13.3%	14.2%	0%
<b>Infections, Asthma and Allergies:</b>			
Tonsil or Adenoidectomy	26.7%	7.1%	40%
Recurrent Otitis Media (ear infections)	57.8%	21.4%	40%
Recurrent Infections, Allergies, Asthma	55.6%	42.9%	40%
Immunological Findings (difficulty fighting infection)	8.9%	0%	0%
<b>Neurologic Findings:</b>			
Seizures	24.4%	14.2%	0%
Mental Retardation			
Mild	46%	75%	80%
Moderate	49%	25%	20%

	Severe	5%	0%	46.2%
	Sleep disturbances	44.4%	28.6%	20%
<b>Abnormalities of the reproductive organs or urinary system</b>				
	Male	50%	100%	66.7%
	Female	37.9%	0%	0%

\*Mb = Megabase (a unit of length used to indicate the size of a piece of DNA)

A careful examination of Table 1 clearly reveals that the individuals with small deletions had a few minor facial features. For many of the facial features, the medium deletions are similar to large deletions; however, there is some striking difference in frequency in several specific traits including: trigonencephaly, strabismus (eyes look in different directions)/nystagmus (involuntary eye movement), palate (roof of the mouth) abnormalities and neck abnormalities.

Similarities among all three groups:

While there were differences among the three groups, it is also striking that there were also many similarities. Overall, prenatal information was limited but based on the collected information, almost all of the mothers had decreased fetal movement during their pregnancy. Approximately 23% of the newborns were not of an appropriate size for the gestational age; large newborns were seen in all the deletions; small newborns were only seen in the medium and large deletions. Likewise, neonatal hypoglycemia (low blood sugar) was seen in about 23% of the subjects studied and was detected in all three groups. All of the subjects had significant hypotonia (low muscle tone) at birth, which resolved as they became older.

It has been clearly established in the medical literature that sex reversal is seen in some males with a 9p deletion (Ottolenghi et al, 2000). Most of the reports in the literature involve single case reports and little has been reported on a larger group of 9p deletion

subjects. It was established that the gene associated with this feature is localized to a region near the end of chromosome 9 (9p24.3), so abnormalities can be seen in all three groups. Overall, we have information on these malformations in 21 males and 42 females. Of the 21 males studied 12 have some degree of genitourinary (reproductive organs or urinary system) abnormality (shown in detail in Table 2); however only one of these subjects presented with complete sex reversal. Only 10 of the 42 females had any genital abnormality. The details are presented in Table 2.

**TABLE 2: GENITOURINARY ABNORMALITIES**

<b>ABNORMAL GENITALIA - DESCRIPTION</b>	<b>NUMBER</b>
<b>MALES<sup>a</sup>:</b>	
Hypospadias (misplaced urinary tract opening of the penis)	4
Testes/Scrotal Abnormality	7
Micropenis	4
Sex Reversal	1
<b>FEMALES:</b>	
Hypoplastic (underdeveloped) Labia Majora	9
Clitoral Hypertrophy (increased in size), Hypoplastic Labia Majora	1

a – Five males demonstrated more than one anomaly and these were indicated separately.

A number of findings involving various types of infections have been reported in all of the individuals with deletions; genitourinary and sinus infections were seen most frequently. All of the subjects had developmental delay/mental retardation; however, the individuals with the smallest deletions appeared to be higher functioning than the individuals with medium or large deletions. The increased impairment in the large deletions could be due to the loss of additional genes that have brain development effects. Sleep disturbances, such as sleep apnea, were seen in all deletion groups in somewhat similar frequency.

Overall, the subjects also all demonstrated related behavior patterns. All demonstrated the classic friendly affectionate behavior, but in addition all of them showed very specific aberrant behavior including aggression, tantrums, obsessive compulsive behavior, hyperactivity, and poor attention span.

We hope that this information is helpful in showing some of the similarities and differences in individuals with 9p deletions. We have tried to summarize this information to make it useful to families. We are available to answer any questions that you or your doctor may have.

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