My daughter Elizabeth turned 27 in March. Along with coping with many other physical and medical challenges, Elizabeth is also visually impaired (see below for a resource that she really loves). Since she is non-verbal, it has always been difficult to determine the amount of impairment she has. We have worked with a developmental ophthalmologist for years and have had varying degrees of success in correcting her vision with glasses.

For those who may not know, even if a patient cannot speak, he or she can receive an effective visual examination. One method is through cycloplegic retinoscopy. After dilating drops are instilled, the doctor uses a retinoscope to shine a light in each eye in a crisscross pattern. During this process, the doctor switches between different lenses to see what type of vision correction, if any, is needed. Elizabeth has had this exam for years, and we always dutifully had glasses made matching the new prescription. Most often she would wear the glasses for a short time and then take them off. Last year was different. After the exam, the doctor was elated; he said, “I think we got it this time!” And sure enough, I think we did. From the beginning, she kept her new glasses on and really seemed to see better. On a recent trip to the zoo, we knew for sure. Elizabeth was amazed by the animals, the colors... just about everything. It was the best day ever. So even though it took years, I'm so glad we kept trying.

Happy Spring Everyone! - Linda

Talking Books and Reading Disabilities

The National Library Service for the Blind and Physically Handicapped (NLS), Library of Congress, administers a free program for individuals who are visually impaired or have a disability that prevents them from using regular print materials. Reading materials, as well as the special playback equipment needed to read the encrypted talking books, are distributed to eligible borrowers through a network of cooperating regional and sub regional libraries. Reading materials and players are circulated by postage-free mail and distributed via the Braille and Audio Reading Download (BARD) service. If you have any questions about the eligibility and certification of those with reading or learning disabilities, would like an application, or would like more information, please contact:

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New Research

Pallister-Killian Syndrome


Pallister-Killian syndrome (PKS) is a genetic condition which results in a variety of symptoms, including facial dysmorphisms, skin discolorations, intellectual disability, developmental delay, congenital heart defects, congenital diaphragmatic hernia (abdominal hernias that occur in fetuses), malformations in the gastrointestinal tract and urinary tract, shortened limbs, and hearing loss. PKS is caused by an additional isochromosome 12p. Typically, a chromosome has a short arm (termed the “p arm”) and a long arm (termed the “q arm”) joined at the middle (the centromere). An isochromosome 12p occurs when chromosome 12 has two p arms, instead of a p and a q. So, the patients have 4 copies of the genes of the short arm of chromosome 12 instead of two. Usually additional isochromosome 12p is found only in some cells whereas other cells may have a normal karyotype.

Prenatal diagnosis is difficult for PKS, and often relies on detection of symptoms (for example, presence of a diaphragmatic hernia) in order to be noticed. Therefore, tools and resources are necessary in order to diagnose PKS more effectively at the prenatal level. This article hopes to help solve this issue by comparing 114 cases of PKS (mostly from the published literature) in order to better characterize the disease prenatally.

In reviewing the data, the most common prenatal findings in PKS patients included polyhydramnios (excessive amniotic fluid in the uterus) and long bone shortening - both of which can be detected by the 17th week of gestation. Fetuses with PKS also typically display fetal macrosomia - they are significantly larger than average. In the second trimester of pregnancy, common prenatal features include ventriculomegaly (ventricles in the brain are enlarged), cardiac septal defects, and calico-pelvic dilatation (widening of the renal pelvis of the kidney).

In terms of prenatal screens, nuchal translucency (NT) might aid as an initial screen for PKS. NT refers to the fluid filled space between the fetal skin and the overlying skin, and enlarged NT usually corresponds with unfavorable prenatal outcomes. In the PKS patients, enlarged NT was often associated with more severe symptoms, such as cardiac heart defects. Though each of these observations is not enough information for a concrete diagnosis of PKS, collectively they can help in detecting the disease at an earlier stage than before.

Producing a proper prenatal diagnosis of PKS can lead to earlier genetic counseling and management of symptoms. If symptoms of PKS are detected, then an amniocentesis can be performed in an attempt to detect the 12p isochromosome specifically.

The article concludes by reiterating the current prenatal profile of PKS: polyhydramnios, long bone shortening, macrosomia, ventriculomegaly, cardiac septal defects, calico-pelvic dilatation, and high NT measurement. More research needs to be conducted to elucidate more prenatal findings; primarily, the distinct facial characteristics of PKS that may be revealed through 3D ultrasound evaluations.
MEIS2


15q14 deletions (deletions occurring within this region of the long arm of chromosome 15) are known to cause cleft palate, intellectual disability, congenital heart defects, and facial dysmorphism. Loss of the MEIS2 gene located within 15q14 has been attributed to these symptoms. To demonstrate the role of the MEIS2 gene, the article reviews 23 patients with either a mutation in MEIS2 alone, or a 15q14 deletion that includes MEIS2. Comparison of these two groups of patients will determine which symptoms are caused by loss of MEIS2, and which may be caused by different genes located within 15q14.

Of the 23 patients studied, 9 had a mutation within MEIS2 alone, and 14 had a 15q14 deletion that encompassed multiple genes including MEIS2. Both groups of patients shared very similar phenotypes, including palatal defects, heart defects, and intellectual disability. It shows that the MEIS2 gene is the main cause of this syndrome. Whether loss of other genes within this region may be contributing to the severity of these heart defects is unknown. For example, ACTC1 - also found within 15q14 - is known cause of septal heart defects.

The magnitude of developmental issues was variable in the 23 patients, and ranged from slight learning problems to severe intellectual disability. Symptom severity was worse in patients with deletions of 15q14 than in patients with MEIS2 mutations alone, likely due to the loss of additional genes within this region. One feature that was present in 15q14 deletion patients and not MEIS2 mutation patients was microcephaly. From these results, it is presumed that other genes within the 15q14 region may be contributing to proper brain development. However, potential genes within this region could not be identified in this study.

These observations further support the assumption that loss of MEIS2 causes symptoms including palatal defects, heart defects, and intellectual disability. In 15q14 deletion patients, loss of this gene likely contributes to these symptoms. However, it should also be mentioned that additional genes within this region may also be contributing to symptom severity.

Coming this summer...

Rare Chromosome Disorder Awareness Week

JUNE 16 - 22, 2019
QUESTIONS:
My child was just diagnosed with trisomy 4p with a duplication and triplication between 4p16.1-15.1. We have not been able to find any other clinical examples of duplications exclusively in the regions our daughter has. Do you know of any other patients with just duplications in those areas, and if so, what abnormalities were noticed?

ANSWER:
This patient is trisomic for a segment of 4p and tetrasomic for a significant part of this segment. Of course, it is a unique situation with more than 10 breakpoints within this segment. Such complex chromosomal abnormalities are the results of some catastrophic events in gametogenesis. CDO has general information articles about chromothripsis and chromoanasynthesis. To the best of my knowledge there are no other published cases of similar rearrangements within 4p.

Usually when we are talking about the function of any gene we know what can happen if this gene is broken or deleted. There are only a few genes where we know the consequences of a duplication of these genes (not a single of such genes reside within this duplication area of 4p). And I doubt that anyone knows the results of a quadriplication for any specific gene.

Most likely such a patient will reveal the manifestations of “trisomy 4p” syndrome. There are no publications about the manifestations in patients with this specific trisomy (without an associated imbalance for another chromosome). In these cases the patients had much smaller duplications. In other cases the patients had tiny duplications (usually < 1 Mb). The vast majority of these patients were only briefly mentioned among other patients reported by the authors. Moreover, in some cases it is not clear whether the clinical abnormalities were caused by the duplication or the duplication was just a random finding unrelated to the phenotype.

Iosif Lurie, M.D., Ph.D. .... continued on page 6
Ask the Doctor: Information contained on this website or in any electronic or written communication should be used for supplemental purposes only. We urge patients and their families to always check with their personal healthcare provider first with any questions or concerns. Your doctor is most knowledgeable about your personal situation.

Please see chromodisorder.org to review our privacy policy.

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ASK THE DOCTOR... CONTINUED

QUESTION:
Follow-up questions: It seems like even microduplications in that area can be extremely damaging. Shouldn't that indicate that the genes in those areas are indeed triplosensitive? Also, the geneticist mentioned chromothripsis and a catastrophic event that occurred in the cell. Is there any indication of when this happened? Did this happen shortly after conception or somewhere along the pregnancy? Did it occur within the egg or sperm before conception?

ANSWER:
Follow-up answer: Catastrophic events leading to multiple breaks and re-unions of chromosomal material may occur both in gametogenesis (ripening of the egg-cells and sperm-cells) and in early embryogenesis. In the last case however we may expect normal clones and clones with rearrangements. Because there are no indications of a normal clone we have to assume that in this case it was an error during gametogenesis. Theoretically the examination of the DNA of the child and both parents allows us to conclude whether this rearrangement is maternal or paternal. However I do not see any practical reasons for such testing. In any case it was a sporadic event.

2. Role of triplicated genes. Clinical manifestations in patients with chromosomal duplications or triplications depend on many factors, and triplicated genes themselves are only one of these factors. Assume that there are several genes A,B,C,D,E, and gene A in normal conditions controls the function of the gene E. Due to duplication (or triplication) we may have the following picture: ABBBCDE or ABBBCDE. Such changes in the spatial structure of the chromosome may disturb the normal A to E control. And lack of this control causes clinical disturbances, although neither A nor E genes are affected. At the same time the duplication or triplication of the B gene looks innocent. The same clinical results may be seen in cases of ABCDDE or ABCDDE. And it is only one example how clinical effects may be independent from the function of triplicated genes.

Best wishes

Iosif Lurie, M.D., Ph.D.
Medical Geneticist
CDO Medical Advisor
Our sweet Madyson has 1q21.1 microdeletion syndrome. It took perseverance, patience and advocacy to finally arrive at her diagnosis. While I was pregnant, I decided against genetic testing because I was in the mind frame that it was used as a tool to choose aborting your child based on an abnormality. I knew I wanted my baby and a test would not change that. Since birth, Madyson was a fighter, and we had noticed so many anomalies diagnosed as facial droop, heart disorder, kidney disorder, short stature, thyroid disorder, vesicoureteral reflux, dental issues, failure to gain weight, anxiety disorder, tibial torsion, femoral anteversion, breath holding spells and a variety of others. She has shown us all what true strength is and continues to light up our world. This precious baby was definitely a blessing from God. - Love Mom

Submit your story for CDO’s Challenging Chromosomes with Courage feature to Linda Sorg at linda.sorg@chromodisorder.org
CDO was honored recently to be able to assist parent and primary caregiver, Alvaro Munoz, in successfully fighting possible deportation to Mexico. His daughter, Shelby, was born with a very rare deletion of chromosome 6q resulting in numerous medical and developmental concerns. Such children need to be under constant supervision of a multidisciplinary team including pediatricians, geneticists, neurologists, speech pathologists, pediatric psychoneurologists and (if necessary) ophthalmologists and ENT-specialists.

From the immigration attorney:

On behalf of our client and his family, we wanted to send you and Dr. Lurie a heartfelt thank you for your support during Alvaro’s case. In large part due to the letter and research you provided us, our client won his case! The immigration judge granted him “cancellation of removal” so that he may remain in the United States with his family as a lawful permanent resident (green card holder). They are thrilled and wanted to send along a message of their deepest gratitude for the excellent work your organization does.

#AMAZINGACHIEVEMENTS
Submit your child’s amazing achievements to be included in our next newsletter by sending to info@chromodisorder.org.

CDO is a non-profit organization providing support & information to individuals and families diagnosed with any rare chromosome disorder. Information contained in this newsletter should be used for informational & supplemental purposes only. Please always contact your personal healthcare provider if you have questions or concerns. CDO accepts no responsibility for the misuse of information contained herein.