Case Report

iMedPub Journals
http://www.imedpub.com/

Journal of Birth Defects

2019
Vol.2 No.1:1

Clinical Recommendations for Chromosome 17q12 Microdeletion Syndrome

Alan Gonzalez, Austin Mc Cuistion, Marcella Muysson, Chibuzo Akalonu and Olubukunola Adesanya*

Department of Pediatrics, Texas Tech School of Medicine, Amarillo, Texas, USA

***Corresponding author:** Olubukunola Adesanya, Department of Pediatrics, Texas Tech School of Medicine, 1400 S Coulter St, Amarillo TX 79106, USA, Tel: 8067431000; E-mail: olu.adesanya@ttuhsc.edu

Receiving date: June 14, 2019; **Accepted date:** August 13, 2019; **Published date:** August 20, 2019

Citation: Gonzalez A, Mc Cuistion A, Muysson M, Akalonu C, Adesanya O (2019) Clinical Recommendations for Chromosome 17q12 Microdeletion Syndrome. J Birth Defects Vol 2, No.1

Abstract

17q12 microdeletion is a rare syndrome that presents with variable features resulting in long term challenges. Early surveillance is necessary for the diagnosis, and the associated with the syndrome. In this case report, we present 17q12 microdeletion syndrome in Di-Di twins born at 31 3/7 weeks gestation. Twin A presented with intellectual disability, patent ductus arteriosus, retrognathia, club feet, and seizure-like activity, and twin B presented with renal cysts, large pericardial effusion, PDA and PFO with left to right shunts. This report provides screening recommendations for renal abnormalities, maturity-onset diabetes of the young type 5 (MODY5), Autism Spectrum Disorder (ASD), developmental delay, intellectual disability, schizophrenia, and Mullerian agenesis to assist pediatricians involved in the medical care of patients with 17q12 microdeletion syndrome.

Keywords: 17q12 Microdeletion; Chromosome; Syndrome; Patients

Abbreviations:

DOL: Day of Life; MODY5: Maturity-Onset Diabetes of the Young Type 5; PDA: Patent Ductus Arteriosus; PFO: Patent Foramen Ovale; HNF1B: Hepatocyte Nuclear Factor 1 Beta; LHX1: LIM Homeobox 1; ECI: Early Childhood Intervention; Mb: Megabases

Introduction

17q12 microdeletion syndrome occurs when a small piece of the long arm on chromosome 17 is deleted. Individuals affected with this syndrome are missing approximately 1.4 megabases (Mb) of one copy of chromosome 17. This syndrome can be inherited in an autosomal dominant fashion, however, the NIH states the majority of cases result from a de novo deletion at 17q121. Diagnosis of 17q12 deletion syndrome is achieved using chromosomal microarray analysis, a cytogenetic technique that detects submicroscopic changes on each chromosome. Worldwide prevalence is unknown; however, some reports suggest a prevalence of 1:20,000, ranking it among one of the ten most common microdeletions in children with unexplained developmental delay [1].

Those affected demonstrate disorders based on the genes deleted from the 17q12 region. One gene lost is hepatocyte nuclear factor 1 beta (HNF1B), previously known as transcription factor 2, which confers higher risk for kidney and urinary tract abnormalities, as well as maturity-onset diabetes of the young type 5 (MODY5). Another gene affected is LIM homeobox 1 (LHX1). Loss of this gene is thought to increase the risk of intellectual disability, Mullerian agenesis, behavioral problems, and psychiatric conditions like schizophrenia [1]. As it is such a rare condition, it is important to analyze cases in order to develop recommendations for management for other patients.

Case Report

A set of dichorionic/diamniotic twins are born with a 17q12 microdeletion at 31 3/7 weeks to a G5P2022, 41 year old mother with a past medical history of depression, obesity, and gestational diabetes mellitus. She had appropriate prenatal care starting at 7 weeks, but used cigarettes throughout the pregnancy and was rubella non-immune **(Figure 1).**

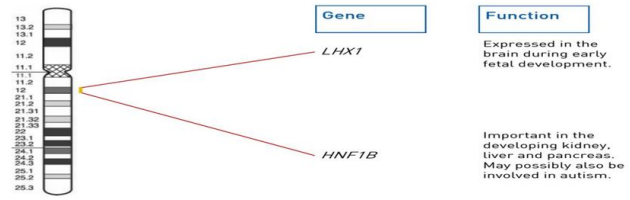

Figure 1: Diagram of chromosome 17 and implicated genes in 17q12 microdeletion syndrome [2].

An emergency C-section was performed at 31 and 3/7 weeks due to preterm labor and 40% discordance and both twins were sent to the NICU. Twin A was noted to have club feet, club hands, and RDS. Twin A was also noted to have microcephaly, micrognathia, and hypotonia. Following the NICU admission, the patient was found to have mild dilation of the lateral ventricles which raised the suspicion for an IVH. A transesophageal echocardiogram showed a medium sized PDA and a small sized ASD with a left-to-right shunt. Both ventricular function and size

were normal. At day of life (DOL) 7, the patient had 15 episodes of apnea and bradycardia that were increasing in severity; this resulted in obtaining a capillary blood gas and decreasing oxygen output from a nasal cannula for possible suppression of respiratory drive. At day of life 7 Twin A had seizure like activity, however EEG was within normal limits. Lumbar punctures and cultures were also unremarkable. Due to the dysmorphic features an array comparative genomic hybridization analysis was performed and revealed a 1.4 Mb loss of 17q12 **(Table 1).**

Table 1 Twin A microarray report.

Significance	Change	Location and Coordinates	Size in Mb or Kb
Pathogenic	Loss	17q12(34,850,785-36,248,926)	1.4 Mb

A microarray was sent for twin B which also found a 17q12 microdeletion, but with a 1.6 Mb size instead **(Table 2)**.

Table 2 Twin B microarray report.

Significance	Change	Location and Coordinates	Size in Mb or Kb
Pathogenic	Loss	17q12(34,652,173-36,248,926)	1.6 Mb

Although twin B also had a 17q12 microdeletion she did not have most of the complications that her sister had. Twin B had a large pericardial effusion, a PDA, and PFO. Trace mitral regurgitation and multiple cysts were found in both kidneys as well.

Discussion

Microdeletions make up a portion of copy-number variants (CNV's) and are classified as recurrent or non-recurrent. Recurrent CNVs occur due to nonallelic homologous recombination with breakpoints in defined regions producing identical deletion in non-related patients. Non-recurrent CNVs have unique breakpoints defined by an individual's genomic architecture1. We believe that our patient had a recurrent CNV due to the similarity in breakpoints in the 17q12 gene.

17q12 microdeletion syndrome presents on a spectrum. One study suggests this is due to incomplete penetrance and variable expressivity which is seen in many genetic disorders2. In this syndrome, almost every case has some form of intellectual disability or behavioral disturbance. Some other commonly observed features include mild facial dysmorphism (high, rounded forehead, arched eyebrows, large head), renal abnormalities, early onset diabetes, developmental delay, Autism Spectrum Disorder (ASD), and reproductive tract abnormalities [1,3]. Less commonly, those affected can present with growth restriction, seizures, and scoliosis.

Renal abnormalities are common in 17q12 microdeletion syndrome. A meta-analysis compiled data from case reports of 43 patients with 17q12 deletions. 21 of the 34 patients that obtained renal imaging reported kidney or urinary tract abnormalities [4]. In our case twin B was found to have renal cysts on ultrasound that spontaneously resolved by 11 months of age.

The twins in this case report are lacking the HNF1B gene and are at risk for developing MODY5, which can result in complications such as hyperosmolar hyperglycemic state or diabetic ketoacidosis; both of which have been reported in case reports of 17q12 microdeletion syndrome patients [5]. In a study following 13 patients from 8 families with the HNF1B mutation, age of onset of diabetes ranged from 13 to 38, with all but two requiring insulin. Atrophy of the exocrine and endocrine pancreas was observed in 5 of 6 patients that required a CT scan [5] **(Table 3)**.

Table 3 Summary of recommendations for commonly seen conditions associated with 17q12 microdeletion syndrome.

Condition	Gene Affected	Recommendation
Renal Abnormalities	HNF1B	Renal Ultrasound, Nephrology referral
MODY type 5	HNF1B	Diabetic screening, Endocrinology referral
Mullerian Agenesis	HNF1B, LHX1	Monitor for amenorrhea at puberty, Gynecology referral, psychosocial interventions
Autism Spectrum Disorder	LHX1	Modified checklist for Autism in Toddlers, developemnt/behavioral or Psychiatry referral
Developmental Delay	LHX1	Monitor development carefully, intervene ealry with speech therapy and early childhood intervention
Intellectual Disability	LHX1	Monitor education carefully, intervene early, special needs referral
Schizophrenia	LHX1	Psychiatry referral

Developmental delay and intellectual disability are very common with this syndrome. The first sign is usually the lack of a social smile in the first two months of life. Later on, the expected sequence of noises, babbling, and jargon may not be seen in the first 18 months of life. Many children still learn to speak if support and stimulation are provided [1]. Referral to Early Childhood Intervention (ECI), speech therapy, and a development/behavioral pediatrician can provide substantial support and early intervention has been shown to improve outcomes [1].

Psychiatric disorders such as ASD and schizophrenia must be assessed in individuals with 17q12 microdeletion syndrome. Additionally, ASD occurs at higher rates in males. Two studies found 100% of males with the syndrome had at least one autistic trait and another study showed that 4/6 boys met full diagnostic criteria [6,7]. High levels of anxiety and neurodevelopmental delay are also associated with the syndrome6. The Modified Checklist for Autism in Toddlers is a valuable screening tool that can be used to direct intervention for these patients [8].

Mayer-Rokitansky-Kuster-Hauser syndrome, or Mullerian agenesis, in females affected by 17q12 microdeletion syndrome occurs due to deletions of HNF1B and LHX1 [9]. Patients with Mullerian agenesis lack the upper vagina as well as the uterus. Those affected initially present with amenorrhea during puberty and according to the American College of Obstetricians and Gynecologists, it is difficult to diagnose prior to puberty as remnants from the Mullerian duct remain and these can be difficult to interpret with ultrasonography. When suspected, these patients should receive close follow up from a gynecologist and receive psychosocial counseling as it is an independent risk factor for depression and anxiety [10].

Conclusion

17q12 microdeletion syndrome is a complicated syndrome which predisposes individuals to a variety of conditions that require monitoring. We recommend that providers who encounter this syndrome be vigilant in assessing for comorbid conditions to improve quality of life of their patients. Further research is needed to determine overall incidence of various associated conditions and the causative genes.

Funding Source

No funding was secured for this study.

Financial Disclosure Statement

The authors have no financial relationships relevant to this article to disclose.

Conflicts of Interest

All authors have indicated that they have no potential conflicts of interest to disclose.

References

1. Mitchel MW, Moreno-De-Luca D, Myers SM (2016) 17q12 Recurrent Deletion Syndrome. In: Adam MP, Ardinger HH, Pagon RA, et al. (eds.) GeneReviews [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2019.
2. George AM, Love DR, Hayes I, Tsang B (2012) Recurrent Transmission of a 17q12 Microdeletion and a Variable Clinical Spectrum. Mol Syndromol 2: 72-75.
3. Roberts JL, Gandomi SK, Parra M (2014) Clinical report of a 17q12 microdeletion with additionally unreported clinical features. Case Rep Genet 2014: 264947.
4. Laffargue F, Bourthoumieu S, Llanas B (2015) Towards a new point of view on the phenotype of patients with a 17q12 microdeletion syndrome. Arch Dis Child 100: 259-264.
5. Bellanné-chantelot C, Chauveau D, Gautier JF (2004) Clinical spectrum associated with hepatocyte nuclear factor-1beta mutations. Ann Intern Med 140: 510-517.
6. Moreno-de-luca D, Mulle JG, Kaminsky EB (2010) Deletion 17q12 is a recurrent copy number variant that confers high risk of autism and schizophrenia. Am J Hum Genet 87: 618-630.
7. Loirat C, Bellanné-chantelot C, Husson I, Deschênes G, Guigonis V, et al. (2010) Autism in three patients with cystic or hyperechogenic kidneys and chromosome 17q12 deletion. Nephrol Dial Transplant 25: 3430-3433.
8. Jin J (2016) Screening for autism spectrum disorder screening for autism spectrum disorder JAMA Patient Page. JAMA 315: 718.
9. Bernardini L, Gimelli S, Gervasini C (2009) Recurrent microdeletion at 17q12 as a cause of Mayer-Rokitansky-Kuster-Hauser (MRKH) syndrome: two case reports. Orphanet J Rare Dis 4: 25.
10. Müllerian agenesis (2013) Diagnosis, management, and treatment. Obstet Gynecol 121: 1134-1137.