ACTAMYOL 2023;XLII:24-30
doi: 10.36185/2532-1900-246

Xp21 contiguous gene deletion syndrome presenting as Duchenne muscular dystrophy and glycerol kinase deficiency associated with intellectual disability: case report and review literature

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The contiguous gene deletion syndromes (CGDS) are rare genomic disorders resulting from the deletion of large segments of DNA, manifested as the concurrence of apparently unrelated clinical features. A typical example of CGDS is Xp21 contiguous gene deletion syndrome that involves *GK* and its neigh-boring genes (usually *DMD* and *NR0B1*) and results in a complex phenotype, which is related to the size of deletion and involved genes. Development delay and intellectual disability are almost a constant feature of patients with CGDS.
We report the case of a boy with Duchenne muscular dystrophy (DMD) and glycerol kinase deficiency (GKD) as part of the contiguous gene deletion syndrome Xp2.1, in association with intellectual disability (ID) in whom multiplex ligation-dependent probe amplification (MLPA) test first identified a hemizygous deletion involving the entire dystrophin gene. Subsequently, the array CGH study identified a maternally inherited hemizygous deletion of the Xp21.2-Xp21.1 region of approximately 3.7Mb that included both *DMD* and *GK* genes confirming the diagnosis of Xp21 CGDS. Moreover, we report a review of the cases published in the literature over the last 20 years, for which a better description of the genes involved in the syndrome was available. Intellectual disability does not appear as a constant feature of the syndrome, reiterating the concept that complex GKD syndrome results from small deletions that affect closely related but separate loci for DMD, GK and adrenal hypoplasia, rather than a single large deletion including all genes.
This case highlights the importance of more in-depth genetic investigations in presence of apparently unrelated clinical findings, allowing an accurate diagnosis of contiguous gene deletion syndromes.

Key words: Xp21 contiguous gene deletion syndrome, *CGDS*, *DMD*, *GKD*, *NR0B1*, *IL1RAPL1*

Received: February 22, 2023
Accepted: March 15, 2023

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How to cite this article: Pizza A, Picillo E, Onore ME, et al. Xp21 contiguous gene deletion syndrome presenting as Duchenne muscular dystrophy and glycerol kinase deficiency associated with intellectual disability: case report and review literature. Acta Myol 2023;42:24-30. https://doi.org/10.36185/2532-1900-246

Introduction

Human glycerol kinase deficiency (GKD) with hyperglycerolemia and glyceroluria, alone or in association with psychomotor retardation, spasticity, dystrophic myopathy and osteoporosis, was first described in 1977 [1,2]. In the subsequent decade, many reports appeared in which the disease was associated with additional phenotypes such as congenital adrenal hypoplasia (ACH), chronic granulomatous disease (CGD), retinitis pigmentosa (RP), McLeod syndrome and/or severe mental retardation, and the disease was named as complex glycerol kinase deficiency (cGKD) [3-8].

In 1985, both X-linked glycerol kinase and X-linked adrenal hypoplasia were mapped to the short arm of the X chromosome, on the region Xp2.1 [9]; the cause of cGKD was attributed to the deletion of the X chromosome [10,11] and the molecular-genetic evidence provided by Franke et al. in 1987 [12]. In 90s the term "contiguous gene deletion syndrome" (CGDS, OMIM 300679) was used to indicate rare genomic disorders that result from the deletion of large segments of DNA that involve multiple adjacent gene loci on a specific chromosome [13-29]. They present as the concurrence of apparently unrelated clinical features, each due to the single gene involved.

Xp2.1 contiguous gene deletion syndrome is due to the partial deletion of the Xp2.1 region [13-29]. Depending on the size of the deletion, other genes responsible for multiple distinct diseases may be involved. Among them, *NR0B1* causing adrenal hypoplasia congenita (AHC), *GK* causing glycerol kinase deficiency (GCD) and *DMD* causing Duchenne muscular dystrophy are the genes most frequently involved. However, the loci for Aland Island eye disease [27,28], chronic granulomatous disease [7], McLeod phenotype [7], retinitis pigmentosa [7], ornithine transcarbamylase deficiency, *CFAP47 (cilia- and flagella-associated protein 47), CYBB (gp91), XK (Kell antigen), RPGR (retinitis pigmentosa GTPase regulator)* [26] have also been reported.

As CGDS first description involved *GK* (OMIM 300474) and the neighboring genes *NR0B1* (OMIM 300473) and *DMD* (OMIM 300377), it was also called *complex* glycerol kinase deficiency (cGKD), characterized by hyperglycerolemia and glyceroluria associated with signs and symptoms of congenital adrenal hypoplasia (AHC) and/or Duchenne muscular dystrophy (DMD) [5,7,11,12,19,21-24].

Glycerol kinase deficiency (GKD) is a rare X-linked recessive metabolic disorder[1,4,30] for which three clinical types are described, based on the age onset of the symptoms: infantile, juvenile and adult form [17]. The clinical findings may vary and include metabolic crisis during starvation, hypoglycemia, seizures, growth restriction, and developmental delay. Childhood GKD, the most common form, may show a more complex clinical presentation, depending on the genes involved along with *GK* [14-16,25]. Juvenile or symptomatic GKD and adult or asymptomatic GKD are instead isolated forms. The clinical features of the former consist in vomiting, acidemia and central nervous system deterioration, including stupor and coma while the latter is detected incidentally with pseudo-hypertriglyceridemia [17].

X-linked AHC, caused by deletion of *NR0B1* gene, is characterized by primary adrenal insufficiency and/or hypogonadotropic hypogonadism (HH) [31]. Adrenal insufficiency has acute infantile onset (average age 3 weeks) in approximately 60% of affected males and childhood onset (ages 1-9 years) in approximately 40%. HH typically manifests in a male with adrenal insufficiency as delayed puberty [31-33].

Duchenne Muscular Dystrophy (DMD) is the most frequent and more severe muscular dystrophy in children. The age of onset is between 3 and 5 years, with delay in the motor skills [34]. Since adolescence, both heart and respiratory muscles are involved in the dystrophic process with evolution towards severe dilated cardiomyopathy and respiratory failure [35-37]. In the vast majority of cases, the patient's mental abilities remain unaffected, though the presence of mental retardation or attentional/autism spectrum disorders has been reported in some studies in up to 30% of patients [38,39], especially in those with deletions located at the 3' of *DMD* gene. Creatine kinase can increase up to 100 times the upper normal limit [40].

Developmental delay has been reported in males with Xp21 deletion when the deletion extends proximally to include *DMD* or when larger deletions extend distally to include both *IL1RAPL1* and *DMD* genes [41-43]. *IL1RAPL1 gene* deletions are often associated with intellectual disability (ID) and, sometimes, autistic spectrum disorder [42-43].

Female carriers of the syndrome may present symptoms related to the specific phenotypes. Two girls have been reported with developmental delay and myopathy, without adrenal dysfunction, due to an Xp21 deletion involving *DMD, GK, NR0B1,* and *IL1RAPL1* genes [44].

Usually, the diagnosis is based on clinical and biochemical findings, and confirmed by genetic analysis.

We report the case of a boy with Duchenne muscular dystrophy (DMD) and glycerol kinase deficiency (GKD) as part of the contiguous gene deletion syndrome Xp2.1. Intellectual disability (ID) was also present. Moreover, we report a review of the cases published in the literature in the last 20 years, for which a better description of the genes involved in the syndrome was available.

Case report

The proband is the only child of non-consanguineous parents with no relevant family history. The pregnancy was complicated by threatened miscarriage during the first trimester. He was born prematurely, at 38 weeks by elective caesarean section and showed a birth weight, length and head circumference of 3200 g (25-50th centile), 51 cm (50-75th centile) and 34.5 cm (50th centile), respectively; the Apgar score was 8 at 1 minute, and 9 at 5 minutes. He presented cyanosis and respiratory distress at birth and a delay in the acquisition of physiological motor milestones: at 7 months, he was still unable to hold his head and to sit up unassisted.

At 10 months the child was addressed to the Pediatric Neurology Unit of the Santobono-Pausilipon Children's Hospital due to global developmental delay associated with high blood transaminases levels. The neurological examination revealed diffuse hypotonia, in particular in the upper and lower limb muscles. The laboratory tests confirmed the elevation of transaminases, CK and lactato-dehydrogenase. Electromyography disclosed a myopathic pattern, while muscle biopsy evidenced a dystrophic pattern with absence of dystrophin staining on immunohistochemistry. Brain MRI showed cerebral periventricular white matter's abnormalities, likely related to immaturity and altered myelination. The detection of hyperCKemia, up to 40 times the upper normal limit, guided the diagnosis of DMD, for which genetic analysis of *DMD* gene was requested. The analysis performed by MLPA technique evidenced the deletion of the entire *DMD* gene.

At the age of 13 months, the child was sent to the Cardiomyology and Medical Genetics of the Luigi Vanvitelli University Hospital for taking care. Physical examination revealed diffuse hypotonia; the child was able to maintain the sitting position, but not to move from supine to sitting position nor to maintain upright position.ECG and echocardiogram were normal. The neuropsychiatric evaluation revealed an IQ score of 25 (< 1st centile), leading to the diagnosis of severe ID. The laboratory findings showed CK: 14576 U/L (normal range: 60-190 U/L); lactate dehydrogenase (LDH): 1742 U/L (normal range:

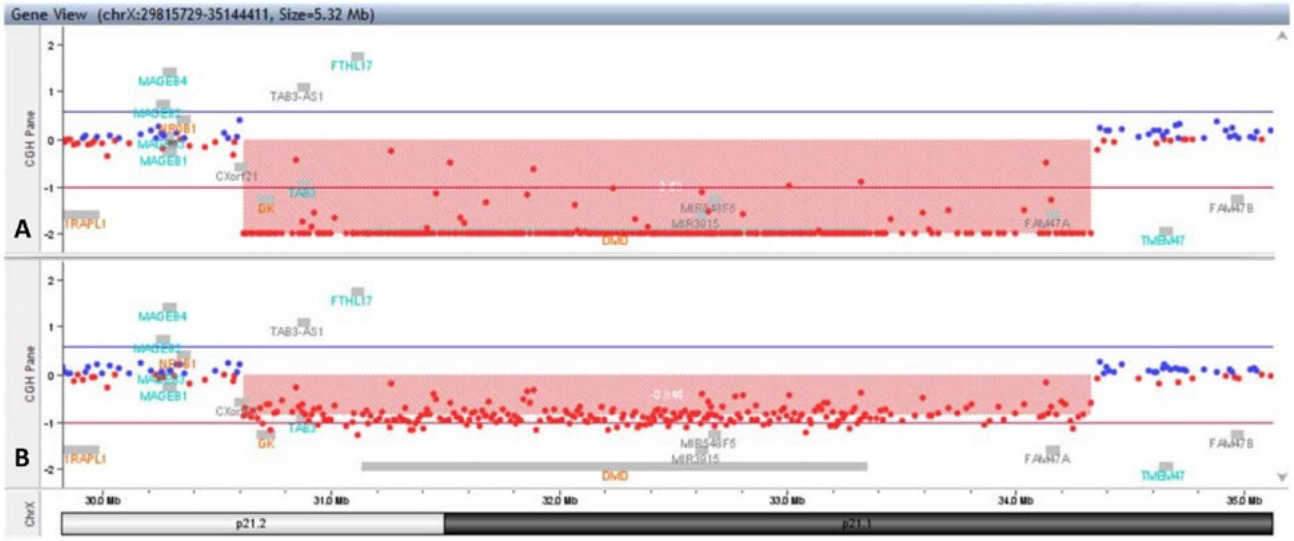

Figure 1. Array 4x180K CGH analysis. The values of the positive or negative Log2 ratio (Y-axis) for each probe in this specific chromosome range (X-axis) are represented by blue and red dots. The red bar corresponds to the deletion of about 3.7 Mb (hg19:ChrX:30615032-34345109), detected with 261 probes in our proband and his carrier mother. The wide deleted region includes the *GK* and *DMD* genes. Array CGH profiles shows: the hemizygous deletion in the proband (A) and the heterozygous deletion in his carrier mother (B).

240-480 U/L); aspartate aminotransferase (AST): 248 U/L (normal range: 5-32 U/L); alanine aminotransferase (ALT): 334 U/L (normal range: 5-33 U/L) and triglycerides 405 mg/dl (normal range: 20-175 mg/dl). The high concentration of serum triglycerides without turbid appearance of the serum sample led to the suspicion of pseudo-hypertriglyceridemia. The patient's urinary glycerol excretion analysed by using gas chromatography-mass spectrometry, was 1082 mM/Mcreatine (normal range: < 1 mM/Mcreat), confirming the suspicion of a CGDS.

After informed consent of parents, an array CGH was performed on the proband and their mother, previously identified as a *DMD* gene carrier. The informed consent is a routine part of clinical testing at Luigi Vanvitelli University Hospital. The consent encompasses testing as well as collecting and using individuals' clinical data for research or publication purposes. The array CGH study identified an approximately 3.7 Mb maternally inherited hemizygous microdeletion of the Xp21.2-Xp21.1 region that included *DMD* and *GK* genes, consistent with the diagnosis of Xp21 contiguous gene deletion syndrome (Fig. 1). The patient started therapy with deflazacort, antioxidants and ACE inhibitors; low-fat diet, physical and speech therapy were recommended. Since then, he did periodic checks every six months and acquired autonomous walking at the age of 4.11. At last observation, at the age of 8.5, he presented waddling gait, lumbar hyperlordosis, mild scoliosis, bilateral Achilles tendon contractures, positive Gowers' sign; moreover, he was unable to run and needed support in standing up from the chair and climbing and descending steps. Cardiac investigation remained normal until 8 years, when myocardial fibrosis of the left ventricular posterior wall was noted at the ECG. He still speaks a few words. Triglycerides remained elevated (two times the upper normal limit).

Discussion

The most common combination of the Xp21 contiguous gene deletion syndrome is the lack of *DMD, GK* and/or *NR0B1* genes (complex GKD). AHC, due to deletions of *NR0B1* gene, is usually the first condition to appear in the cGKD with symptoms of adrenal insufficiency [14-16].

The lack of *DMD* and *GK* genes only represents a minority of cases, affecting less than 5% of patients of complex GKD [4-7,15-16]. The diagnostic suspicion of the infantile form of GKD can be in presence of complete deletion of the DMD gene together with the incidental finding of increased serum triglyceride levels, and confirmed by array CGH study.

Elevated serum triglyceride levels and glyceroluria are caused by the deficiency of glycerol kinase, the enzyme responsible for the phosphorylation of glycerol resulting from the breakdown of triglycerides leading to accumulation of glycerol in the blood [24]. Hyperglycerolaemia can lead to hypoglycemia and osmotic dehydration [45].

The Xp21 contiguous gene deletion syndrome is often difficult to diagnose in its early stage because of different clinical characteristics attributable to the single-gene involved in the deletion [45,46]. The physicians should consider the Xp21 contiguous gene deletion syndrome in infants with dystrophinopathy and pseudo-hypertriglyceridemia.

Global developmental delay and intellectual disability often occur with GCDS. Table I lists the fourteen cases of the syndrome presenting with the DMD phenotype and published since the 2000s. In almost all the reported cases the sequencing of genes involved in the Xp21 region, spanned distally the *DMD* gene and included *GK* (3 documented cases), *NR0B1* (3 cases) and *IL1RAPL1* (3 cases) genes (Fig. 2). The deletions of the *DMD* locus were all located in the distal part of the gene after exon 44 (1 case) and after exon 62 (2 cases). DMD patients who present these mutations generally are at

Table I. Age of onset, initial clinical presentation and genetic information in reported cases with CGDS involving *DMD*, *GK*, *NR0B1* and *IL1RAPL1* genes.

Patient's number	Involved Genes (centromere-telomere direction)	Deletion Size	Age at clinical presentation	Symptoms	Metabolic Laboratory findings	CK values in U/L	Reference
1	***DMD***; other genes were not investigated	n.r.	19 days	Dehydration; intermitting vomiting; developmental delay; global weakness; calf hypertrophy; reflexes absent, ID	↓ natraemia,17-OH-progesterone ↑ kalaemia, triglycerides, urinary glycerol	2.507	Ramanjam V. et al., 2010
2	***DMD***; other genes were not investigated	n. r.	prenatal	Hypotonia; waddling gait; difficulty in climbing stairs, ID	↓ 17-OH-progesterone ↑ triglycerides, urinary glycerol	5.307	Ramanjam V. et al., 2010yes
3	***DMD*** (exons 62-66), GK, NR0B1	n. r.	42 months	Nausea; vomiting, global development delay; unable to walk, go upstairs, run fast; Gower's sign; calf hypertrophy, ID	↓ natraemia,cortisol, cholesterol, apolipoprotein-B, HDL- ↑ kalaemia, LDH, ALT, triglycerides, α-OH-butyratedehydrogenase	5.798	Ma H. et al., 2004
4	***DMD***, GK	n. r.	4 months	Failure to thrive; global developmental delay; axial hypotonia; distal hypertonia, ID	↑ LDH, ALT, AST, triglycerides, urinary glycerol	10.818	Jamroz E. et al.,2010
5	***DMD***, GK	3.7Mb	7 months	Global development delay; hypotonia; unable to walk, to go upstairs, to sit, ID	↑ LDH, ALT, AST, triglycerides, urinary glycerol	14.576	**Present Case**
6	***DMD*** (exons 45-79), GK	n. r.	36 days	Failure to thrive; global developmental delay; difficulty in walking, getting up from the seated position; Gower's sign; calf hypertrophy	↓ natraemia, glycaemia, cortisol, aldosteron; 17-OH-progesterone ↑ kalaemia, ACTH, renin, triglycerides, urinary glycerol	12.395	Rathnasiri A. et al.,2021
7	***DMD***, GK, NR0B1	n. r.	11 days	Salt loss with lethargy; vomiting; metabolic acidosis; progressive muscle weakness, ID	↓ natraemia, glycemia; ↑ kalaemia, triglycerides, serum and urinary glycerol	n.r.	Pantoja-Martines J. et al., 2007
8	***DMD***, GK, NR0B1	n. r.	48 days	Hypotonia, growth retardation, vomiting, dark skin	↓ natraemia,17-OH-progesterone ↑ kalaemia, ALT, AST, triglycerides, α-OH-butyratedehydrogenase, urinary glycerol	1.586	Tao N. et al., 2002
9	***DMD***, GK, NR0B1	3.88Mb	18 days	Weight <3rd percentile; dehydration; dysmorphic facial features	↓ natraemia, glycemia; ↑ kalaemia, triglycerides, urinary glycerol; α-OH-butyrate; LDH, ALT, AST	1.586	Korkut S. et al., 2016
10	***DMD*** (partial), GK, NR0B1, ***IL1RAPL1*** (part)	n. r.	36 days	Difficulty to feed, vomiting, weight loss, hypotonia, dehydration	↓natraemia, glycemia; ↑ kalaemia, triglycerides, urinary glycerol	5.758	Korkut S. et al., 2016
11	***DMD***, GK, NR0B1, ***IL1RAPL1***	n. r.	7 months	Global developmental delay; pronounced axial hypotonia, ID	↑ triglycerides, serum and urinary glycerol	12.829	Sanz-Ruiz I. et al., 2009
12	***DMD*** (exons 62-79), GK, NR0B1, ***IL1RAPL1***	n. r.	1 month	Generalized hypotonia; inadequate breast-feeding; failure to thrive; decreased skin turgor; sitting with support	↓ natraemia; ↑ kalaemia, ALT, AST, triglycerides, LDH	7.019	Sevim U. et al., 2011
13	***IL1RAPL1***, MAGEB1-4, ROB,CXorf2, GM, AP3K71P,FTHL1, ***DMD***, FAM47A, TMEM47, FAM47B	5.8Mb	data not available				Liu L. et al., 2021
14	***DMD***, GK, CFAP47, CYBB, XK,RPGR	7.5Mb	19 days	Macrosomia, neonatal sepsis; liver and lung abscesses	↑ ALT, AST, triglycerides	1.115	Bi S. et al., 2023

Legend: n.r. = not reported; DMD = Duchenne muscular dystrophy; GK = glycerol kinase; nR0B1 = nuclear receptor superfamily 0, group B, member 1; IL1RAPL1 = interleukin 1 receptor accessory protein-like 1.

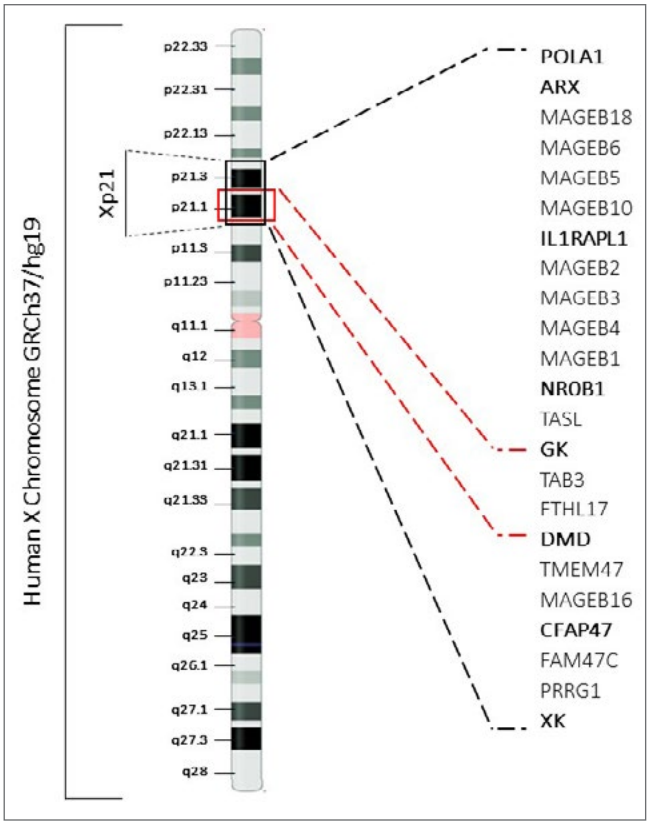

Figure 2. Gene map of region Xp21 on human X chromosome. The black box corresponds to the Xp21 contiguous gene deletion syndrome region, which includes twenty-three genes. The deletion identified in our proband can be visualized in the red box, which involves a region of 3.7 Mb (chrX:30615032-34345109) and encompasses *DMD* and *GK* genes. OMIM genes are in bold.

higher risk of developing cognitive or other /signs of interest of the CNS [38,39]. A decrease in full-scale intelligence quotient (FSIQ < 70) has been reported in about 30% of DMD patients compared with the population's mean, while a severe impairment with a FSIQ < 50 in approximately 3.0% [38]. Zhang et al. showed that nearly all patients with deletions involving *DAX1*, but not *DMD*, had mental retardation if *IL1RAPL1* (interleukin-1 receptor accessory protein-like gene 1) gene was deleted [41]. *IL1RAPL1* is highly expressed in the postnatal brain, specifically in hippocampus, suggesting a specialized role in memory and learning abilities. However, despite such extensive deletions, cases who do not present the phenotypic manifestations associated with the lack of the related genes have been reported in the literature. For example, in the patient described by Seltzer et al. in 1989 [8], the specific activity and kinetics of muscle GK were normal, but the subcellular distribution of muscle GK was altered; on the contrary liver GK had less than 10% of normal activity and showed markedly altered kinetics, suggesting that muscle and liver GK are genetically distinct. Based on these findings, they suggested that complex GKD syndrome results from small deletions that affect closely related but separate loci for DMD, GK and adrenal hypoplasia, rather than a single large deletion including all genes [9]. In our patient, in which the deletion is limited to the Xp21 region including DMD and GK loci, we retain that the clinical picture of a severe intellectual disability can be the result of multiple concurrent causes, such as the complete deletion of *DMD* gene, prematurity and brain suffering due to neonatal respiratory distress.

In conclusion, determining the extent of the deletion by an appropriate molecular analysis has relevant implications on establishing the appropriate medical management that demands the need for a multidisciplinary team approach. Making the exact diagnosis is also useful in the identification of the female carriers and in the genetic counselling. The case here reported highlights the importance of more in-depth genetic investigations in presence of apparently unrelated clinical findings, allowing an accurate diagnosis of contiguous gene deletion syndromes.

Acknowledgements

We are grateful to the patient's family for collaboration.

Conflict of interest statement

The Authors declare no conflict of interest.

Funding

The study did not receive any fund.

Authors' contributions

AP: formal analysis and writing the original draft; EP, MEO: formal analysis and preparation of the figure; MS, LPa: clinical evaluation; VN: data curation and validation; LP: conceptualization, methodology, supervision, writing - original draft, writing - review & editing.

Ethical consideration

The study was conducted according to the rules of the Helsinki declaration. As indicated in the text the informed consent was achieved at the time of hospitalization. The consent encompasses genetic testing as well as collecting and using individuals' clinical data for research or publication purposes.

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