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Hyperkinetic Movement Disorders in Congenital Disorders of Glycosylation.

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Conflicts of interest: nothing to report.

Approval: Study protocol was approved by our local ethics committee at the University of Catania, Italy. This observational study was based solely on information and investigations that were carried out as part of the routine clinical care of the patients. Informed consent was obtained from adult patients or underage patients' parents or guardians.

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Abstract

Background. Congenital Disorders of Glycosylation (CDG) represent an increasing number of rare inherited metabolic diseases associated with abnormal glycan metabolism and disease onset in infancy or early childhood. Most CDG are multi-systemic diseases mainly affecting the central nervous system.

Objectives. The aim of the current study was to investigate hyperkinetic movement disorders in patients affected by CDG and to characterize phenomenology based on CDG subtypes.

Methods. Subjects were identified from a cohort of patients with CDG who were referred to the University Hospital of Catania, Italy. Patients were evaluated by neurologists with expertise in movement disorders and videotaped using a standardized protocol.

Results. A variety of hyperkinetic movement disorders was detected in eight unrelated CDG patients. Involuntary movements were generally observed early in childhood, maintaining a clinical stability over time. Distribution ranged from a generalized, especially in younger subjects, to a segmental/multifocal involvement. In patients with phosphomannomutase 2 CDG, the principal movement disorders included dystonia and choreo-athetosis. In patients affected by other CDG types, the movement disorders ranged from pure generalized chorea to mixed movement disorders including dystonia and complex stereotypies.

Conclusions. Hyperkinetic movement disorder is a key clinical feature in patients with CDG. CDG should be considered in the differential diagnosis of childhood-onset dyskinesia, especially when associated with ataxia, developmental delay, intellectual disability, autism, or seizure disorder.

Introduction

Glycans are ubiquitous molecules implicated in fundamental biological processes such as cell-cell interactions, protein secretion, protein signaling, and protein folding.[1] Congenital Disorders of Glycosylation (CDG) represent a group of rare inherited diseases of glycan metabolism associated with defects in the synthesis and processing of glycoprotein and glycolipid glycans.[1] CDG are heterogeneous disorders ranging from a single-organ disease to multisystem diseases with prominent central nervous system involvement. The prevalence of CDG is estimated to be 0.1-0.5/100.000.[2] However, the estimated carrier frequency of phosphomannomutase 2 (PMM2) deficiency, the most common CDG, ranges between 1/20.000 and 1/77.000.[3,4]

Biochemically, CDG can be classified as: *a.*defects in protein N-glycosylation or asparagine-linked glycosylation (ALG), dichotomized in CDG-type I (CDG-I) and CDG-type II (CDG-II) based on different subcellular localizations of glycosylation defects; *b.*defects in protein O-glycosylation; *c.*defects in glycosphingolipid and in glycosylphosphatidylinositol anchor glycosylation; *d.*defects in multiple glycosylation pathways and in other pathways, as observed in defects of the conserved oligomeric Golgi (COG) complex subunits.[1,5-7]

Diagnosis of CDG is based on biochemical screening, which includes serum transferrin (Tf) glycoform analyses by IsoElectroFocusing (IEF) as well as Matrix-Assisted Laser Desorption/Ionization Mass Spectrometry (MALDI-MS)[8]. For all CDG, genetic work-up combined with glycomic analyses have an increasingly important role for the diagnosis.[5,9]

The most characteristic neurological presentation for CDG, especially for PMM2-CDG, is cerebellar ataxia.[10-12] Hyperkinetic movement disorders are anecdotally mentioned among neurological aspects of human glycosylation disorders.[2,13] However, to our knowledge, they were not yet systematically investigated nor characterized in patients with CDG.

The aim of the current study was to investigate the presence of hyperkinetic movement disorders in a cohort of patients affected by CDG, in order to characterize phenomenology based on CDG subtypes.

Materials and Methods

Study population

Study subjects were selected from a cohort of patients with CDG who were diagnosed at and/or referred to the Child Neurology Unit and to the Referral Center for Inherited Metabolic Diseases at the "*A.O.U.Policlinico-Vittorio Emanuele*" University Hospital of Catania, Italy.

During the last 30 years, more than 50 patients with CDG were referred to our Center. We enrolled for this study all subjects who had their follow-up visits from January to December 2017. During each visit, standardized clinical examinations including neuropsychological assessments and routine laboratory analyses were performed in all patients. Neurophysiological assessments including electroencephalography (EEG), electroretinogram/visual evoked potentials and electromyography/nerve conduction velocity studies, together with brain magnetic resonance imaging (MRI) were available for all patients.

All patients underwent biochemical screening by serum Tf IEF and/or capillary electrophoresis. Apolipoprotein-CIII (Apo-CIII) analyses and total plasma N-glycan structure characterizations were also performed using *ad hoc* protocols by MALDI-MS analyses.[8] Molecular diagnosis was achieved by Sanger analyses for PMM2 gene and by targeted next generation or whole exome sequencing analyses.

Patients referred to the Center for their follow-up visits during the observational period were evaluated by neurologists with expertise in movement disorders from the Neurology Clinic at the University Hospital of Catania for their phenomenological characterization. Patients were clinically examined and videotaped based on a standardized protocol.[14] Home-made videos were also reviewed. Videos were analyzed by a panel of experts in movement disorders and a final consensus of phenomenology was sought.

The study was based solely on information and investigations that were carried out as part of the routine clinical care of the patients. Informed consent was obtained from adult patients or underage patients' parents or guardians.

Results

We enrolled all the eight unrelated patients with CDG who were evaluated by our Referral Center during the observational period, including six males and two females, with age ranging from two to 28 years. Six patients had CDG-I including four patients with PMM2-CDG, one patient with ALG6-CDG, and one patient with ALG8-CDG. One child was diagnosed with combined N-and O-glycosylation defect due to COG5-CDG. One patient with CDG-I had no molecular diagnosis as yet although targeted next generation sequencing was performed (CDG type Ix). The study sample represented the 14% of subjects affected by

CDG who were referred to our center since the last 30 years, including 45 subjects with PMM2-CDG and 11 individuals with CDG different than PMM2.

All patients exhibited a variety of abnormal involuntary movements which were noted during clinic visits and documented by videos (**Supplemental Material Video**). According to parents' report and retrospective analyses of clinical files, for all patients involuntary movements were observed early in childhood starting from the first months of life, maintaining a clinical stability over time in terms of severity. Distribution ranged from a generalized, especially in younger subjects at the time of the evaluation, to a segmental/multifocal involvement. Detected movement disorders were prominently continuous and exacerbated by fatigue or emotional stress as principal precipitants for all subjects. Demographic and genetic data, prominent neurological features, hyperkinetic movement disorders phenomenology, neuroimaging data, systemic features and laboratory findings of study patients with CDG have been summarized in **Tab.1**.

Patients with PMM2-CDG exhibited prominent cerebellar ataxia with generalized muscular hypotonia and delayed psychomotor development. Most of them required support to walk except for Patient #4, who presented a milder phenotype. Neuroimaging on MRI was principally characterized by cerebellar atrophy involving hemispheres and the cerebellar vermis (**Fig.1A-B**). In our patients with PMM2-CDG, we observed that hyperkinetic involuntary movements, especially dystonia and choreo-athetosis, were dominant clinical features. Dystonia, both generalized (Patient #2) or segmental/multifocal (Patient #1, #3, #4), was present in all four patients with PMM2-CDG, and choreo-athetosis was the most common hyperkinetic movement disorder in such patients. Involuntary movements were mostly generalized or they principally affected the limbs (Patient #1, #2, #3).

Patient with ALG6-CDG was affected by early myoclonic encephalopathy of infancy.[15] Neurological examination revealed the presence of severe developmental delay with flaccid tetraparesis and axial hypotonia. As for PMM2-CDG, generalized choreo-athetosis associated with segmental dystonia were also observed in this patient (Patient #5).

In other CDG types, we recorded peculiar phenotypic features. ALG8-CDG patient was clinically characterized by a childhood-onset epileptic encephalopathy associated with severe intellectual disability and ataxia. Neuroimaging on MRI showed dilated Virchow-Robin spaces in the supratentorial white matter and in the basal ganglia and mild cerebral and cerebellar atrophy (**Fig.1C-D**). Clinically, a pure generalized chorea was observed in this patient, with a "bizarre" choreic-ataxic gait superimposed by exaggerated arm swing which may represent parakinesia (Patient #6).

Patient with COG5-CDG was affected by severe psychomotor disability with axial hypotonia and flaccid tetraparesis. Neuroimaging on MRI documented diffuse white matter atrophy, increased T2 signal of the external capsule and increased T1 signal of the posterior thalami and dentate nuclei (**Fig.1E-F**). MALDI-TOF MS analyses showed a defect in sialylation and to a minor extent in galactosylation of total plasma N-glycans (**Supplemental Material Fig.2**). Clinically, generalized chorea combined with complex stereotypies consisting in paroxysmal tonic extensions of the arms and flexion-extensions of the legs were observed in this subject (Patient #7).

Simple or complex stereotypies were observed in three out eight study subjects. They seemed especially common when accompanied by severe intellectual disability (Patient #2, #7, #8).

Concerning pharmacological treatment, patients with epilepsy received symptomatic therapy as monotherapy, specifically levetiracetam in the case of ALG8-CDG patient, or antiepileptic drugs polytherapy, specifically valproate, carbamazepine and clonazepam in the case of ALG6-CDG patient. No specific therapy for dyskinesia was undertaken due to lack of evidences in CDG.

Discussion

In our sample of patients affected by CDG, we documented a broad spectrum of hyperkinetic movement disorders such as generalized choreoathetosis, segmental/multifocal and generalized dystonia, and motor stereotypies. All CDG patients evaluated during the observational period presented clinically-detectable involuntary movements with more than one movement disorder, suggesting that the occurrence of hyperkinetic movement disorders in CDG may be overall underestimated. Similar to other rare childhood-onset movement disorders, many of these patients with CDG were initially misdiagnosed as syndromic intellectual disability, autism or dyskinetic cerebral palsy.[16]

By the date, dyskinesia in CDG has been only sporadically reported as additional clinical feature. Descriptions are principally limited to single CDG patients and reported in different glycosylation pathways.[2,13] Available data on involuntary movements other than ataxia and related tremor as well as epileptic myoclonus in human glycosylation disorders are presented in **Tab.2**. Hyperkinetic movement disorders have been only documented in a few dozen patients, a small estimate with respect to the thousand of patients diagnosed in Europe[2], being mostly reported in PMM2-CDG[10,17-19] and deficiency of N-glycanase 1 (NGLY1).[20] Overall, choreo-athetosis and dystonia together with stereotypies were the prevalent documented hyperkinetic movement disorders across the different CDG subtypes.

PMM2-CDG is characterized by global developmental delay, ataxia, truncal titubation, ocular motor abnormalities and prominent cerebellar atrophy with onset as early as the first months of age.[6,10] Most patients with PMM2-CDG have a severe, disabling condition as a result of which become wheel-chair dependent or able to walk only with support.[12] Some patients may have a milder phenotype, as illustrated in Patient #4.[9,21]. While dystonia was anecdotally reported in PMM2-CDG,[10,17-19] it was detected in all four patients in this study, associated with choreo-athetosis.

ALG6-CDG is the second most common type of CDG. Clinically, patients with ALG6-CDG exhibit global developmental delay, hypotonia and ataxia. Most of them have epilepsy and intractable seizures are often observed. Non-neurological symptoms include failure to thrive, enteropathy, coagulation defects and hand anomalies. Brain structural changes associated with ALG6-CDG are represented by cerebral and cerebellar atrophy.[2] Dystonia and generalized choreo-athetosis represented relevant clinical features in our patient with ALG6-CDG. Presence of dyskinesia has been rarely highlighted in other reported patients.[22-23]

ALG8-CDG is characterized by distinct facial dysmorphisms, brachy-camptodactyly and usually severe systemic involvement including liver disease, enteropathy, renal tubulopathy and ocular pathology.[24-25] Neurological manifestations are variable but usually include severe psychomotor disability, seizures, and hypotonia.[26] Unsteady ataxic gait with normal brain and cerebellar imaging was described in two sibs with a mild ALG8-CDG phenotype.[27] About half of fifteen ALG8-CDG patients reported so far died precociously.[26] Our Patient #6 was affected by a childhood-onset epileptic encephalopathy associated with severe intellectual disability, ataxia and pure generalized chorea. To our knowledge, movement disorders including chorea have never been previously reported in ALG8-CDG (**Tab.2**).

COG-CDG are due to mutations in genes encoding COG subunits leading to impaired vesicular trafficking and functioning of both O- and N- glycosylation machinery in the Golgi apparatus. Patients with mutations in *COG1-COG2* and *COG4-COG8* genes have been reported, usually with a severe clinical phenotype.[2,28] In one study seven patients with COG5-CDG mutations have been described, showing a wide clinical spectrum from mild to very severe neurological impairment.[29-31] In our Patient #7 with COG5-CDG, clinical features included marked growth retardation, psychomotor disability, generalized chorea and stereotypies. In our sample of patients, in addition to COG5-CDG, stereotypic movements combined with intellectual disability were leading clinical features in Patient #8 with CDG-Ix.

Based on our report, we then suggest that CDG should be taken into account in the differential diagnosis of hyperkinetic movement disorders in childhood, and their characterization may help clinicians in suspecting a specific CDG subtype when associated with other clinical features. Considering there are more than 100 identified forms of CDG with a broad range of phenotypic presentation, there is a need for a clinical characterization of this pathological entity. Looking at possible key features for the diagnosis, in CDG patients seems to be peculiar the combination of hyperkinetic movement disorders with developmental delay, dysmorphism and a multisystemic involvement. Differential diagnosis with CDG should consider all conditions combining neurodevelopmental issues and mixed movement disorders including dystonia, chorea, tremor and stereotypies (**Supplemental Material Fig.3**). Dystonia in childhood, particularly when isolated, is often caused by single gene mutation, such as *DYT1* or *DYT6*,[32] or ascribed to L-dopa-responsive dystonia,[33] but combined dystonia, as usually observed in CDG, may have various genetic, metabolic, or structural etiologies.[16,34] In the context of childhood-onset recessive chorea, CDG should be differentiated from disorders related to monoamine and amino acidergic neurotransmitter

metabolism, in particular, aromatic L-amino acid decarboxylase deficiency and disorders of monoamine transport.[33,35] Childhood-onset simple and complex stereotypies in the context of CDG should be instead differentiated from those observed in heredo-degenerative disorders,[36] as well as from stereotypies observed in the setting of early-onset epileptic encephalopathies with behavior disorder.[37-38]

The pathophysiological mechanisms of dyskinesia in CDG remain poorly understood. A link between PMM2-CDG and *CACNA1A* mutations linked to ataxia has been suggested.[39] Due to the documented extensive cerebral involvement in these disorders, it is quite likely that both basal ganglia and the cerebral cortex are directly involved in the pathogenesis of movement disorders in CDG.

One limitation of our study is the focus on a single-center, hospital-based sample of patients with CDG. Nevertheless, because of the paucity of reports available on literature about this topic, our patients add to the expanding phenotype of CDG. Moreover, the treatment of disabling dyskinesia in CDG has not been systematically investigated yet, thus further studies are needed.

In conclusions, hyperkinetic movement disorders represent key clinical features in patients with CDG. CDG should be considered in the differential diagnosis of dyskinesia in childhood.

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Fig.1. Brain MRI scans of patients with PMM2-CDG Patient #4 (A-B), ALG8-CDG Patient #6 (C-D) and COG5-CDG Patient #7 (E-F).

Legend: A.Axial FLAIR; B.Sagittal T1 FSE; C.Axial T2 SE Dual; D.Sagittal T1 SE; E.Axial T2; F.Sagittal T1. Arrows show vermis (A) and cerebellar hemispheres (B) atrophy in Patient #4; dilated basal ganglia Virchow-Robin spaces (C) and mild cerebellar atrophy (D) in Patient #6; increased signal of the external capsule (E), posterior thalami and dentate nuclei (F) in Patient #7.

Tab.1. Clinical-instrumental data of study patients with CDG.

Patient No.	**#1**	**#2**	**#3**	**#4**	**#5**	**#6**	**#7**	**#8**
Demographical data								
Age (years)	2	3	13	28	10	11	2	9
Sex (M/F)	F	M	M	M	M	M	M	F
Genetic data								
CDG subtype	PMM2-CDG	PMM2-CDG	PMM2-CDG	PMM2-CDG	ALG6-CDG	ALG8-CDG	COG5-CDG	CDG-Ix
Mutations	p.R141H/A108V	p.R141H/D223N	p.R141H/N216I	p.L32R/R141H	p.A84T/A84T	p.P69L/P69L	p.A235Vfs*6/p.I780dup	Unknown
Prominent neurological features								
Psychomotor retardation	+	+	+	+	+	+	+	+
Intellectual disability	Mild. (I.Q.=69)	Severe (I.Q.<35)	Severe (I.Q.=45)	Moderate (I.Q.=52)	Severe (I.Q.<35)	Severe (I.Q.=40)	Severe (I.Q.<35)	Severe (I.Q.<35)
Microcephaly	-	+	+	+	+	-	+	+
Hypotonia	+	+	+	+	+	+	+	+
Ataxia	+	+	+	+	-	+	-	-
Eye	Nystagmus, squint	Nystagmus, squint	Nystagmus, squint	Nystagmus, squint	Poor fixation, absent pursuit, squint	Squint	Poor fixation, squint	Poor fixation, squint
Retinitis pigmentosa	-	-	+	+	-	-	-	+

Epilepsy	-	-	-	-	+	+	-	-
Febrile seizures	+	+	+	-	+	+	-	-
Stroke-like episodes	-	-	+	+	-	-	-	-
Peripheral neuropathy	-	+	+	+	-	-	-	-
Behavioral disturbance / A.S.D	-	-	-	-	-	+	-	+
Movement Disorders Phenomenology								
Dystonia	Lower limbs	Generalized	Multifocal	Multifocal	Upper limbs	-	-	-
Athetosis	Lower limbs	Generalized	Upper limbs	-	Generalized	-	-	-
Chorea	Lower limbs	Generalized	Upper limbs	-	Generalized	Generalized	Generalized	-
Stereotypies	-	+	-	-	-	-	+	+
Neuroimaging								
Cerebellar hypoplasia	+	+	+	+	-	+	-	+
Cerebral Atrophy	-	-	-	-	+	+	-	-
White Matter Changes	-	-	+	-	-	+	+	-
Other	-	Pons atrophy	Pons atrophy	-	-	Dilated basal ganglia Virchow-Robin spaces	Increase T1 signal external capsule, posterior thalami and dentate nuclei	Pineal cyst

Systemic Features								
Failure to thrive	+	+	+	-	+	-	+	+
Facial Dysmorphism	+	+	+	+	+	+	+	+
Skin	Fat pads	Inverted nipples	-	-	-	-	-	Fat pads, inverted nipples
Skeletal	-	Pectus excavatum	Pectus excavatum, thoracic scoliosis	-	Thoracic scoliosis	Brachydactyly, joint laxity	Bell thorax	Clubfoots
Heart	-	-	-	-	-	-	-	-
Liver / Spleen	-	Hepatomegaly / Splenomegaly; increased transaminases	Normal-high transaminases	-	Normal-high transaminases	Normal-high transaminases	Hepatomegaly / Splenomegaly Normal-high transaminases	-
Gastro-intestinal	-	Diarrhea, ascites	-	-	Gastroesophageal reflux	Diarrhea	Enteropathy	-
Endocrine	-	-	-	+	-	-	-	-
Urogenital	-	Renal hyperechogenicity; bilateral cryptorchidism	Bilateral cryptorchidism.	-	Bilateral cryptorchidism	Unilateral cryptorchidism	Neurogenic bladder bilateral cryptorchidism	-
Laboratory Findings								
Transferrin glycosylation	Type I	Type I	Type I	Type I	Type I	Type I	Type II (defect in sialylation and galactosylation)	Type I

Coagulopathy	-	Increase PT, aPTT; Decrease FXI, AT-III	Increase PT, aPTT; Decrease FIX, FXI AT-III, Prot C	Decrease FVIII and AT-III	Decreased FXI, AT-III, Prot S	Increase PT, aPTT; Decrease FXI, AT-III	Decrease Prot C, Prot S	Increase PT, PTT; Decrease FXI.
Other	-	Microalbuminuria, low serum albumin	-	Low TSH	Glycosuria, galactosuria	-	Recurrent infections, low TBG	-

Notes: CDG: Congenital Disorders of Glycosylation. PMM2: phosphomannomutase 2. ALG6: asparagine-linked glycosylation 6. ALG8: asparagine-linked glycosylation 8. COG: conserved oligomeric Golgi complex 5. M: Male. F: Female. I.Q.: Intelligence Quotient. A.S.D.: Autistic Spectrum Disorder. PT: Prothrombin Time. aPTT: activated Partial Thromboplastin Time. FVIII, -IX,-XI: coagulation Factor VIII,-IX, XI. AT-III: Antithrombin III. Prot C, -S: Protein C, -S.

Tab.2. Available data on hyperkinetic movement disorders associated with CDG.

Disorder (#OMIM)	Gene	Function	Movement Disorder (Reported Cases)
N-Linked Pathway			
PMM2-CDG #212065	*PMM2*	Conversion of Man-6P to Ma-1P	Dystonia (N=3)[17,19]; stereotypies (N=4)[10,18,40]; tremor (N=2)[18]
ALG6-CDG #603147	*ALG6*	Glucosyltraferase	Tremor (N=1)[2,23]
DPAGT1-CDG #608093	*DPAGT1*	GlcNAc Transferase	Tremor[13]
ALG13-CDG #300884	*ALG13*	GlcNAc Transferase	"Extrapiramidal signs"[13]
MGAT2-CDG #212066	*MGAT2*	GlcNAc Transferase II	Stereotypies (N=1)[41]
DDOST-CDG #614507	*DDOST*	Subunit of the OST complex	Tremor[13]
N- and O-Linked Pathways			
TRAPPC11-CDG #614138	*TRAPPC11*	Transport protein particle complex 11	Chorea, tremor[2]
NGLY1 Deficiency #615273	*NGLY1*	Deglycosylates N-glycoproteins via cleavage at the GlcNAc-Aparagine linkage	Choreo-athetosis, dystonia, myoclonus, tremor (N=12)[20]
GPI anchor synthesis			
Hyperphosphatasia intellectual disability syndrome #239300	*PIGV*	Mannosyltransferase	Athetosis, dystonia[13]
Autosomal recessive GPI-anchor deficiency #614080	*PIGN*	GPI ethanolamine phosphate transferase	Tremor[13]; chorea (N=1)[13,42]
Autosomal recessive GPI-anchor deficiency # 611655	*PGAP1*	Lipid remodeling steps of GPI-anchor maturation	Stereotypies[2]

Other			
Amish infantile epilepsy or Salt and Pepper syndrome **#609056**	*ST3GAL5*	Sialyltransferase	Choreo-athetosis (N=1)[2,13,43]; tremor[2]
Complex Hereditary Spastic Paraplegia **#609195**	*B4GALNT1*	GalNAc Transferase 1	Dystonia[13]

Notes: data include both reported cases from referred studies as well as not-specified descriptions from reviews. CDG: Congenital Disorders of Glycosylation. D.D.: Developmental Delay. I.D.: Intellectual Disability. PMM2: phosphomannomutase 2. ALG6: asparagine-linked glycosylation 6. DPAGT1: Dolichyl-Phosphate N-Acetylglucosaminephosphotransferase 1. ALG13: asparagine-linked glycosylation 13. MGAT2: mannosyl (alpha-1,6-)-glycoprotein beta-1,2-N-acetylglucosaminyltransferase. DDOST: Dolichyl-Diphosphooligosaccharide--Protein Glycosyltransferase Non-Catalytic Subunit. TRAPPC11: trafficking protein particle complex 11. NGLY1: N-glycanase 1. PIGV: phosphatidylinositol glycan anchor biosynthesis class V. PIGN: phosphatidylinositol glycan anchor biosynthesis class N. PGAP1: post-GPI attachment to proteins 1. ST3GAL5: ST3 beta-galactoside alpha-2,3-sialyltransferase 5. B4GALNT1: Beta-1,4 N-acetylgalactosaminyltransferase 1. *Additional table references:* [40] Neumann LM, et al. Eur J Pediatr. 2003;162:710-713. [41] Jaeken J, et al. Arch Dis Child 1994;71:123-127. [42] Maydan G, et al. J Med Genet 2011;48:383-389. [43] Boccuto L, et al. Hum Mol Genet 2014;23:418-433.