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Review and metabolomic profiling of unsolved case reveals newly reported autosomal dominant congenital disorder of glycosylation, type Iw formerly thought to only be an autosomal recessive condition

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ABSTRACT

Autosomal dominant congenital disorder of glycosylation (CDG) type Iw (OMIM# 619714) is caused by a heterozygous mutation in the *STT3A* gene. Most CDGs have an autosomal recessive (AR) mode of inheritance, but several cases with an autosomal dominant (AD) form of an AR CDG have been recently identified. This report describes a 17-year-old male who was referred to the Undiagnosed Diseases Network (UDN) with a history of macrocephaly, failure to thrive, short stature, epilepsy, autism, attention-deficit/hyperactivity disorder, mild developmental delay, intermittent hypotonia, dysmorphic features, and mildly enlarged aortic root. Trio exome sequencing was negative. His biochemical workup included normal plasma amino acids, ammonia, acylcarnitine profile and urine organic and amino acids. His UDN genome sequencing (GS) identified a previously unreported *de novo STT3A* variant (c.1631A > G: p.Asn544Ser). This variant removes a glycosylation site and was predicted to be destabilizing by structural biology modeling. The patient was formally diagnosed by the UDN Metabolomics Core as having an abnormal transferrin profile indicative of CDG type Iw through metabolomic profiling. We report here an affected male with phenotypic, molecular, and metabolic findings consistent with CDG type Iw due to a heterozygous *STT3A* variant. This case highlights the importance of further testing of individuals with the phenotypic and metabolic findings of an AR disorder who are heterozygous for a single disease-causing allele and can be shown to have a new AD form of the disorder that represents clinical heterogeneity.

1. Introduction

Glycosylation is a process of adding sugar to lipid and proteins in various pathways. Congenital disorders of glycosylation (CDGs) result from heterogenous defects in these pathways [1]. CDGs are categorized by the defect in the glycosylation pathway in which they reside and include N-glycosylation, O-glycosylation, and lipid glycosylation and glycosylphosphatidylinositol (GPI) anchor glycosylation, and defects affecting multiple glycosylation pathways [6].

To date, there are 163 genes linked to 193 disorders of CDGs [4]. Most of these disorders are autosomal recessive (AR), but some autosomal dominant (AD) and X-linked (XL) have been reported. CDGs can impact many different organ systems but are notorious for causing neurological and developmental phenotype. The patient in this report had been on a 14-year diagnostic odyssey and was ultimately diagnosed with Congenital disorder of glycosylation (CDG), type Iw, AD due to a *de novo* variant in *STT3A*. STT3 is a catalytic subunit within the oligosaccharyltransferase (OST) complex that is encoded by STT3A [3,6].

This report highlights the importance of keeping candidate variants in AR conditions on the list of differential diagnoses in unsolved cases as

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AD modes of inheritance may be reported in the future.

2. Case presentation

The patient discussed in this case was referred to the UDN at age 12 for a history of dysmorphic features, macrocephaly, failure to thrive, short stature, autism, attention deficit hyperactivity disorder (ADHD), intermittent hypotonia, and history of epilepsy. His parents were 19 and 23 years old at the time of birth and were in good health. Pregnancy was complicated by a maternal episode of supraventricular tachycardia (SVT), subchorionic hemorrhage at 10 weeks, and partial placental abruption at 20 weeks' gestation. Prenatal ultrasound noted a single umbilical artery (SUA). At birth, the patient was full-term but had intrauterine growth restriction (IUGR) with birth weight of 2693 g and length of 48 cm (Fig. 1). The SUA prompted an ultrasound of the kidneys that was normal. Newborn screening was also normal. There were no similarly affected family members, and his parents and two brothers were in good health.

The patient had mildly delayed developmental milestones. He first walked at 16 months of age and used single words at 18 months but talked in sentences by 2–1/2 years of age. He achieved bladder and bowel control at 4 and 6 years of age. He had an individualized educational program (IEP) in school, and he received occupational, speech, physical and behavioral therapies. Neuropsychologic evaluation confirmed the following diagnoses: ADHD, anxiety disorder, and autism spectrum disorder. Neuropsychological testing revealed an overall IQ of 80. He was diagnosed with focal epilepsy at 4 years of age and tonic-clonic seizures at 6 years of age of which he eventually did well on antiepileptics and was able to come off medications at age 8. There have been no concerns for recurrence of seizures since discontinuing antiepileptics. Electroencephalograms have been subsequently normal.

Prior to referral to the UDN, the patient had a comprehensive genetic work up including Fragile X, Karyotype, and Chromosomal Microarray Analysis (CMA) all of which were non-diagnostic. Metabolic work-up included normal Serum NH4, urine amino acids, urine organic acids, acylcarnitine profile, serum lactic acid, and lactate/pyruvate. He had a *POLG* (Gln1236His) variant which did not explain his constellation of symptoms. Mitochondrial DNA sequence and deletion/duplication analyses of blood lymphocytes were negative. MRI and MRS of the brain revealed asymmetric maxillary hypoplasia but were otherwise normal. His skeletal survey showed significant maxillary overbite, but no other abnormalities. An echocardiogram was performed at 11 years of age after an episode of tachycardia and the maternal family history of SVT. The study noted that both the ascending aorta and aortic root were mildly prominent (Z score + 1.45; and + 1.74) but, subsequently both measured within normal range for his age.

At 12 years of age, the patient returned to genetics clinic, where he was found to have prominent facial features including significant

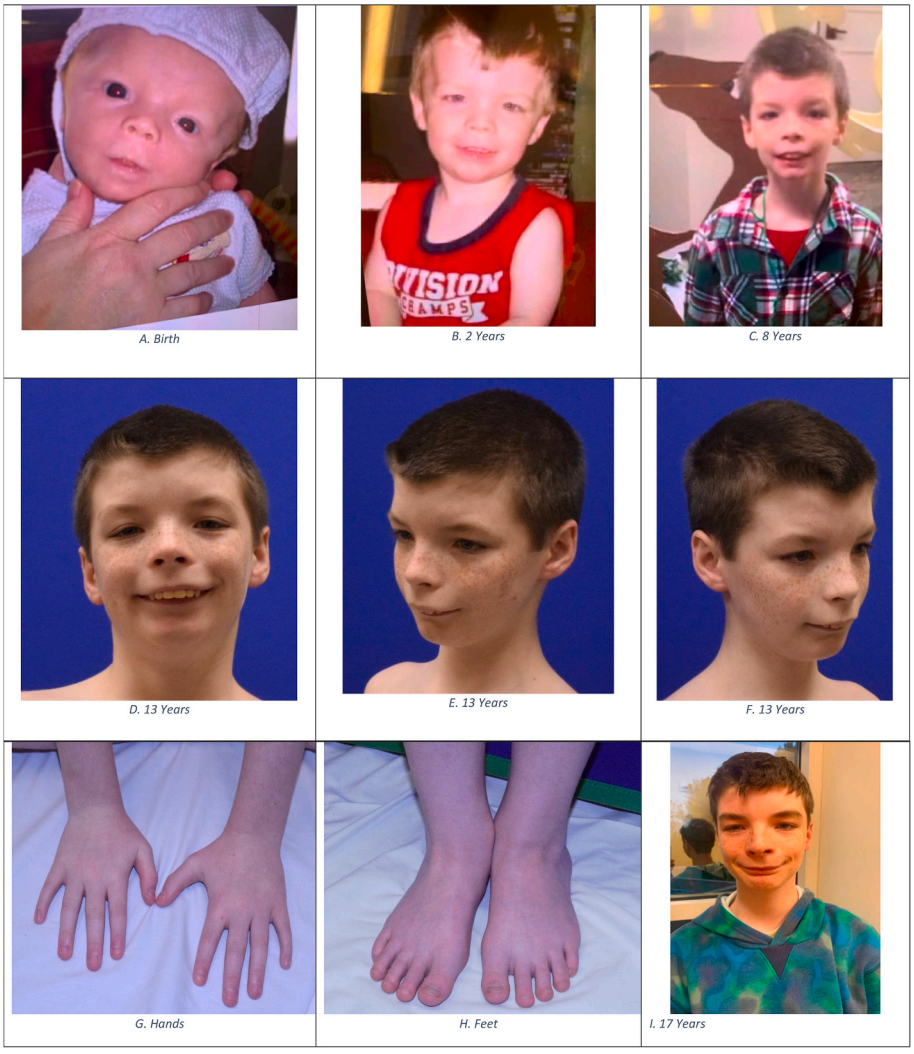

Fig. 1. Proband photos A. Facial profile at birth B. Facial profile at 2 years old C. Facial profile at 8 years old D. Facial profile at 13 years old E. Left profile at 13 years old F. Right profile at 13 years old G. Hands H. Feet I. Facial profile at 17 years old.

overbite, high arched palate, flat philtrum, hypertelorism, down slanting and slit like palpebral fissures, long mouth with thin upper lip, widows' peak hair pattern, attached earlobes, inverted nipples, mild cutaneous syndactyly between some of the fingers, and pes planus (Fig. 1). He was significantly short and had macrocephaly. His height was 133 cm (1 %ile), weight: 28 kg (1.25 %ile), and head circumference 56.5 cm (>98 %ile). He was evaluated by endocrinology because of deceleration both in height and weight between the ages of 6–8 years. He had normal bone maturation, T4/TSH, and IGF-1 results. His constellation of findings prompted testing of the *FGD1* gene (Aarskog-Scott syndrome) which was negative. His Exome Sequencing (ES) trio testing in 2018 was also negative. Subsequently he was referred to the UDN. Informed consent under National Institutes of Health IRB protocol 15-HG-0130 was obtained prior to research.

As part of the UDN workup, he underwent Genome Sequencing (GS) trio analysis by the Vanderbilt UDN team using Emedgene online software (www.emedgene.com) in which coding, non-coding, and copy number variants (CNVs) were interrogated. Candidate gene variants were evaluated and prioritized based on likelihood of pathogenicity, variant frequency (0.001 or less), inheritance pattern, and phenotypic overlap with proband. Segregation studies in additional unaffected siblings eliminated a number of candidates. Our top candidate following these analyses was a *de novo STT3A* variant in exon 14 c.1631A > G; p.Asn544Ser confirmed by Sanger sequencing. The CADD Score was 27.7 suggesting being in the 1 % most deleterious substitution in the human genome with cutoff 20 or greater [9]. No other pathogenic or potentially pathogenic variants were discovered in STT3A.

At the time of the report, *STT3A* had only been associated with AR CDG type 1w (OMIM 615596) (*Clinical Synopsis - #615596 - CONGENITAL DISORDER OF GLYCOSYLATION, TYPE Iw, AUTOSOMAL RECESSIVE; CDG1WAR - OMIM*, [2]). Clinical features of CDG Iw (AR) include intellectual disability, absent speech, microcephaly, failure to thrive, seizures, hypotonia, and cerebellar atrophy. Since a second *STT3A* heterozygous variant was not identified his p.Asn544Ser variant was not deemed to be a definitive explanation for his constellation of symptoms at the time but was significant because it was *de novo* and suspected to be deleterious.

3. Structural biology modeling

STT3A is the catalytic subunit of the mammalian oligosaccharyltransferase (OST) complex, specifically of the OST-A complex which catalyzes the co-translational transfer of a preassembled, high-mannose oligosaccharide onto the asparagine residue of the glycosylation sequon, Asn-X-Thr/Ser. A high resolution, cryoEM structure of human OST-A complex reveals that the Asn544 residue falls within a flexible linker joining two helices in the ER luminal portion of STT3A [7]. Biophysical modeling of the effects of the p.Asn544Ser variant predicts the serine substitution to be moderately destabilizing in the monomeric form of STT3A (ddG = 2 Rosetta Energy Units; REUs are a computational estimate of free energy of folding which scales with the experimental metric of kcal/mol) (Fig. 2). Importantly, in the wild type form, Asn544 is also a site of translational modification, and is one of only three N-glycosites characterized in STT3A (Asn537, Asn544, Asn548) [10]. Because N-

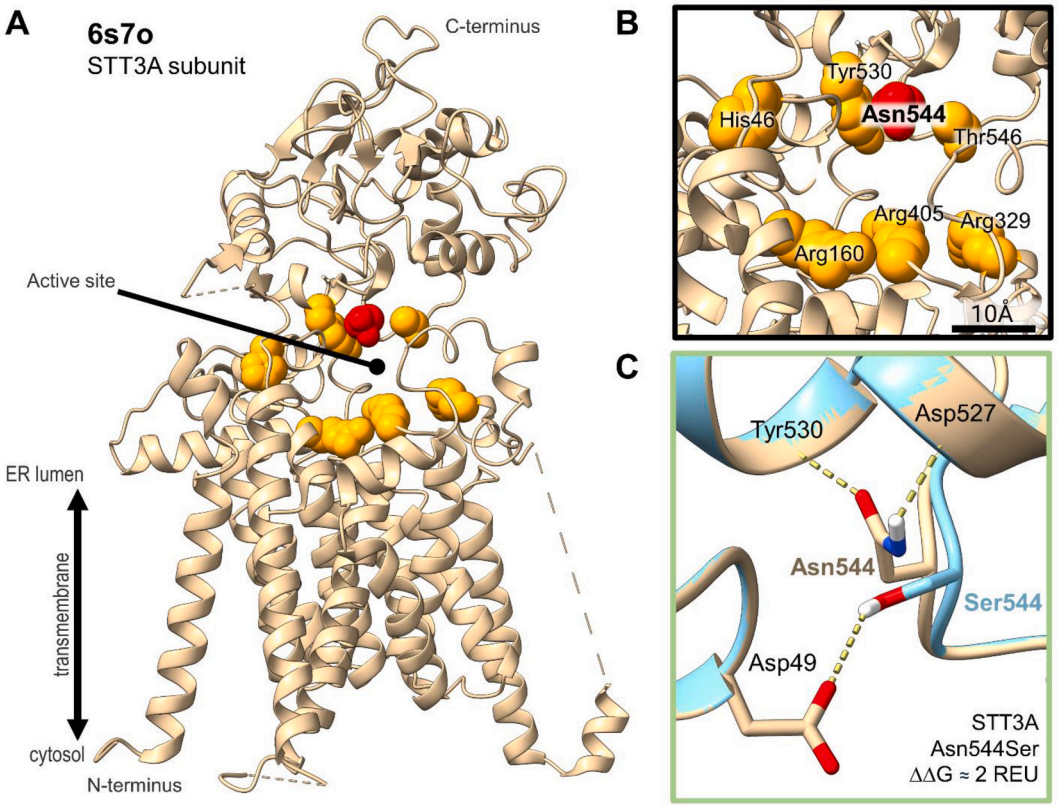

Fig. 2. Asn544Ser mutation is predicted to destabilize STT3A.
A: The STT3A subunit of the 3.5 Å resolution cryo EM structure of the human oligosaccharyltransferase complex OST-A (6s7o). Highlighted amino acid side chains indicate Asn544 (red) and the sites of six, previously identified pathogenic missense variants (orange) in Wilson et al. [10]. B. Detail of the context of Asn544 within the active site of STT3A. Each of the six known pathogenic variants occur within less than 15 Å of Asn544. C. Biophysical modeling of the *de novo* variant (Asn544Ser). The superimposed structural images show both the canonical Asn544 residue (tan) and proband's *de novo* variant, Ser544 (blue) in their local, energy-minimized, conformational contexts. The *de novo* variant results in the replacement of two internal hydrogen bonds (dashed yellow lines) between the sidechain of Asn544 and Asp527 and Tyr530, with a single hydrogen bond between Ser544 and Asp49. Ser544 is predicted to destabilize STT3A relative to Asn544 by approximately 2 REUs (Rosetta Energy Unit; REUs are a computational estimate of free energy of folding which scales with the experimental metric of kcal/mol).

linked glycosylation is a co-translational process that contributes to protein folding and stability, deletion of N-glycosites could alter any number of STT3A's physical properties including conformation, stability, solubility, and complex formation. Therefore, while p.Asn544Ser may modestly affect the structural stability of STT3A, the loss of any of the three N-glycosites is likely to have larger and more wide-ranging functional consequences. Both findings are consistent with previous observations showing normal STT3A protein levels, yet abnormal patterns of glycosylation [10].

4. Metabolomic profiling

In view of possible CDG type 1w, STT3A, and the heterozygous p.Asn544Ser *STT3A* variant found by GS, a plasma specimen was sent to the UDN Metabolomics Core for affinity chromatography electron spray ionization chromatography mass spectrometry analysis of transferrin (Tf) and apolipoprotein CIII (ApoCIII) glycoforms. Hypoglycosylate Tf and/or ApoCIII are biochemical markers for CDG [5]. A qualitative assessment of endogenous proteins and glycoforms using multiply charged ion spectra obtained by mass-range scanning indicated that mono-oligosaccharide transferrin was increased (Fig. 3). In addition, the mono-oligo Tf/di-oligo Tf ratio was moderately elevated (Table 1) and consistent with a CDG type 1 Tf profile. Based on laboratory experience, Mono-oligo/Di-oligo ratios for CDG type 1 can range in value (0.13–3.44; 1st-99th%-ile), placing our patient's result at the lower end of but within known CDG type 1 Tf profiles.

5. Diagnosis

In reviewing our patient's findings, a new report was found that linked *STT3A* to an AD form of CDG, type Iw in which 16 individuals were reported with neuro-muscular-skeletal findings and single *STT3A* pathogenic variants [10]. The patients, ranging in age from infancy to age 55, shared a phenotype of variable skeletal anomalies, short stature, macrocephaly, and dysmorphic features. Overlapping features of our patient with those in the report include macrocephaly, thin upper lip, wide nasal bridge, inverted nipples, mild to moderate motor delay, hypotonia, speech delay, short stature, and a type 1 transferrin glycosylation profile (Table 2).

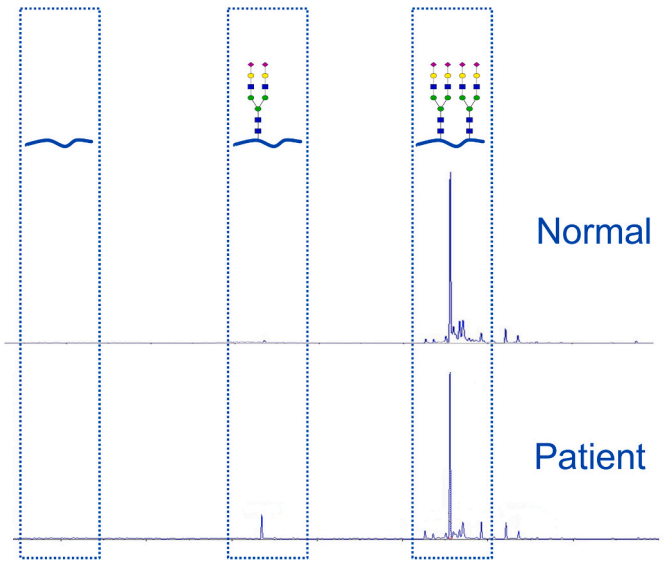

Fig. 3. The transferrin glycosylation analysis demonstrating an increased mono-oligosaccharide Tf level in this patient's plasma specimen consistent with a CDG-type I profile.

Table 1
Affinity Chromatography-Mass Spectrometry of Tf and ApoCIII Isoform Ratios.

Analyte	Measured Value	Reference Values
Mono-oligo/Di-oligo Tf Ratio	**0.15**	≤ 0.06
A-oligo/Di-oligo Tf Ratio	0.008	≤ 0.011
Tri-sialo/Di-oligo Tf Ratio	0.05	≤ 0.05
ApoCIII-1/ApoCIII-2 Ratio	1.46	≤ 2.91
ApoCIII-0/ApoCIII-2 Ratio	0.20	≤ 0.48

Table 2
Comparison of clinical features of patients with autosomal dominant STT3A-CDG in Wilson et al. [10] and our proband.

Reported features [10]	Our proband
Age at diagnosis: 3 weeks-55 years old	16
Sex: n = 8 in females; *n* = 8 in males	Male
Macrocephaly	+
Short palpebral fissures	Downslanting & slit like palpebral fissures
Thin upper lip	+
Wide nasal bridge	+
Prognathism	–
Inverted nipples	+
Motor delay	+
Speech delay	+
Hypotonia	+
Hypertonia	–
Muscle cramps	–
Skeletal abnormalities	+ (maxillary overbite, syndactyly & pes planus)
Autism	+
Type 1 transferrin glycosylation profile	+
Not Reported	ADHD

6. Discussion

We reviewed our patient's case considering this publication and felt the newly described AD form of STT3A-related CDG overlaps well with his clinical features. His physical characteristics were consistent with the reported patients in Wilson et al. [10], including dysmorphic features, hypotonia, speech delay, motor delay, inverted nipples, short stature, macrocephaly, and autism. Interestingly, our patient has ADHD which has not been described in STT3A-CDG, AD. Notably our patient's previously unreported p.Asn544Ser variant in *STT3A* clusters around the catalytic site of STT3A similarly to those reported in Wilson et al. [10] (Fig. 2). For further confirmation of the diagnosis, our colleagues at the UDN Metabolomics Core performed CDG tandem mass spectrometry and found a Tf profile consistent with that of CDG Type Iw similar to those reported in Wilson et al. [10].

Our patient returned to genetics at 17 years of age. He had the same facial features that had been previously observed (Fig. 1). Growth parameters at the time resulted in height: 167.7 cm (13 %ile), weight: 53 kg, (6 %ile), and head circumference: 57 cm (98 %ile). He anticipates orthognathic surgery to correct his significant overbite but is otherwise doing well.

We could not find any current treatment protocols or clinical trials for STT3A-CDG (CDG-Iw). Frontiers in CDG Network information was given to the family as a resource for support [8]. We recommend CDG Natural History protocols at the National Institutes of Health for further follow up.

7. Conclusion

CDG represents a diverse, heterogenous, and growing group of disease that continue to evolve in molecular basis and modes of inheritance. This report highlights an affected male with a *de novo* variant in *STT3A*, whose phenotypic, molecular, and metabolic findings are

consistent with an AD form of CDG type Iw. Structural biology analysis indicates that the loss of residue Asn544 removes 1 of only 3 known N-glycosites in an active-site. The metabolic profiling by the UDN metabolomics core revealed that the mono-oligo Tf/di-oligo Tf ratio was moderately elevated and consistent with a CDG type 1 Tf profile. This case shows the importance of further studies of heterozygous candidate variants cases thought to be an AR condition because they may represent new AD disorders that are examples of clinical heterogeneity.

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Kimberly M. Ezell: Writing – review & editing, Writing – original draft, Investigation, Formal analysis, Conceptualization. **Yutaka Furuta:** Writing – review & editing, Writing – original draft. **Devin Oglesbee:** Writing – review & editing, Writing – original draft, Investigation, Formal analysis, Conceptualization. **Eniko K. Pivnick:** Writing – review & editing, Writing – original draft. **David Rinker:** Writing – review & editing, Writing – original draft, Investigation. **Jonathan H. Sheehan:** Writing – review & editing, Writing – original draft, Investigation. **Rory J. Tinker:** Writing – review & editing, Writing – original draft. **Rizwan Hamid:** Supervision, Investigation, Formal analysis. **Joy D. Cogan:** Supervision, Investigation, Formal analysis. **Lynette Rives:** Investigation, Formal analysis. **Serena Neumann:** Writing – review & editing, Writing – original draft. **Brian Corner:** Formal analysis. **John A. Phillips:** Writing – review & editing, Writing – original draft, Supervision, Investigation, Formal analysis.

Declaration of competing interest

The authors declare no conflicts of interest.

Data availability

Data will be made available on request.

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