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Troyer Syndrome

Synonym: SPG20

Emma Baple, MBBS, MRCPCH, PhD[1] and Andrew Crosby, PhD[1]

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Summary

Clinical characteristics

Troyer syndrome is characterized by progressive spastic paraparesis, dysarthria, pseudobulbar palsy, distal amyotrophy, short stature, and subtle skeletal abnormalities. Most affected children exhibit delays in walking and speech and difficulty in managing oral secretions, followed by increased lower-limb spasticity and slow deterioration in both gait and speech. Mild cerebellar signs are common. The most severely affected individuals have choreoathetosis. Emotional lability / difficulty in controlling emotions and affective disorders, such as inappropriate euphoria and/or crying, are frequently described. Life expectancy is normal.

Diagnosis/testing

The diagnosis of Troyer syndrome is established in an individual with characteristic clinical findings. Identification of biallelic pathogenic variants in *SPART* confirms the diagnosis if clinical features are inconclusive.

Management

Treatment of manifestations: Antispasticity drugs; daily physical therapy; occupational therapy, assistive walking devices, and ankle-foot orthotics as needed; antidepressant or mood stabilizer medication for individuals with emotional lability.

Surveillance: Neurologic and developmental/cognitive assessments; monitoring for dysphagia to reduce the risk of aspiration.

Agents/circumstances to avoid: Dantrolene should be avoided in persons who are ambulatory as it may induce irreversible weakness, which can adversely interfere with overall mobility.

Author Affiliation: 1 Medical Research Research, Innovation, Learning and Development Wellcome Wolfson Centre University of Exeter Medical School Exeter, United Kingdom; Email: e.baple@exeter.ac.uk; Email: a.h.crosby@exeter.ac.uk.

Genetic counseling

Troyer syndrome is inherited in an autosomal recessive manner. At conception, each sib of an affected individual has a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier. Carrier testing for at-risk relatives and prenatal testing for pregnancies at increased risk are possible if both pathogenic variants have been identified in an affected family member.

Diagnosis

Suggestive Findings

Troyer syndrome **should be suspected** in individuals with the following findings:

Clinical features

- Childhood-onset spastic paraplegia
- Dysarthria
- Persistent drooling
- Symmetric amyotrophy of the small muscles of hands and feet
- Short stature
- Emotional lability

Additional clinical features

- At birth: low/low-normal birth weight, relative macrocephaly, triangular face shape, poor feeding
- Early infancy / childhood: delayed walking, delayed speech, swallowing difficulties
- Pyramidal signs: hyperreflexia, extensor plantar responses
- Extrapyramidal signs: mild choreoathetoid movements
- Cerebellar signs: dysdiadochokinesia, mild intention tremor
- Skeletal abnormalities: *pes cavus*, mild *talipes equinovarus*, kyphoscoliosis
- Mild to moderate intellectual disability

Imaging features on brain MRI. White matter abnormalities, particularly in the temporoparietal periventricular area (3/3 affected individuals)

Establishing the Diagnosis

The diagnosis of Troyer syndrome **is established** in a proband with childhood-onset spastic paraplegia, distal amyotrophy, short stature, and/or biallelic pathogenic variants in *SPART* identified by molecular genetic testing (see Table 1).

Molecular genetic testing approaches can include a combination of **gene-targeted testing** (single-gene testing, multigene panel) and **comprehensive genomic testing** (exome sequencing, genome sequencing) depending on the phenotype.

Gene-targeted testing requires that the clinician determine which gene(s) are likely involved, whereas genomic testing does not. Because the phenotype of Troyer syndrome is broad, individuals with the distinctive findings described in Suggestive Findings are likely to be diagnosed using gene-targeted testing (see Option 1), whereas those in whom the diagnosis of Troyer syndrome has not been considered are more likely to be diagnosed using genomic testing (see Option 2).

Option 1

When the phenotypic and laboratory findings suggest the diagnosis of Troyer syndrome, molecular genetic testing approaches can include **single-gene testing** or use of a **multigene panel**:

- **Single-gene testing.** Sequence analysis of *SPART* detects small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. Perform sequence analysis first. If only one or no pathogenic variant is found, perform gene-targeted deletion/duplication analysis to detect intragenic deletions or duplications.

  Note: Targeted analysis for pathogenic variant c.1110delA can be performed first in individuals of Amish ancestry [Patel et al 2002].

- **A hereditary spastic paraplegia multigene panel** that includes *SPART* and other genes of interest (see Differential Diagnosis) is most likely to identify the genetic cause of the condition while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*. Of note, given the rarity of Troyer syndrome, some panels for hereditary spastic paraplegia may not include this gene. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests.

  For an introduction to multigene panels click here. More detailed information for clinicians ordering genetic tests can be found here.

Option 2

When the diagnosis of Troyer syndrome is not considered because an individual has atypical phenotypic features, **comprehensive genomic testing** (which does not require the clinician to determine which gene[s] are likely involved) is the best option. **Exome sequencing** is the most commonly used genomic testing method; **genome sequencing** is also possible.

For an introduction to comprehensive genomic testing click here. More detailed information for clinicians ordering genomic testing can be found here.

Table 1. Molecular Genetic Testing Used in Troyer Syndrome

Gene [1]	Method	Proportion of Pathogenic Variants [2] Detectable by Method
SPART	Sequence analysis [3]	100%
	Gene-targeted deletion/duplication analysis [4]	Unknown, none reported

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on allelic variants detected in this gene.
3. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
4. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include a range of techniques such as quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.

Clinical Characteristics

Clinical Description

Troyer syndrome is characterized by both developmental and neurodegenerative processes. Symptoms are usually apparent in early childhood and progress slowly. The cardinal features of Troyer syndrome include developmental delay, spastic paraparesis, dysarthria, distal amyotrophy, and short stature. To date, 36 individuals with Troyer syndrome have been reported, including 21 individuals from an Old Order Amish population in Ohio, USA [Patel et al 2002, Proukakis et al 2004, Manzini et al 2010, Tawamie et al 2015, Butler et al 2016, Dardour et al 2017, Spiegel et al 2017].

Onset. Clinical features that may be recognized from birth in the Amish, where the condition occurs at an increased frequency, include low birth weight, relative macrocephaly, triangular face shape, and poor feeding. Neurologic features become more apparent in early childhood and progress slowly.

Early developmental milestones. In the Old Order Amish, Proukakis et al [2004] reported that the presenting feature in most individuals was a delay in reaching early gross motor and speech and language milestones (walking and talking) compared to unaffected sibs. Twenty of the 21 individuals were delayed in walking (age range 12-22 months; mean age 16.1 months). The age at which they started talking ranged from seven to 36 months, with a mean age of 17.5 months. In those whose milestones were not noticeably delayed, the character of the gait and/or speech was the first abnormality reported.

Neurologic features. Troyer syndrome leads to gait ataxia and progressive spastic paraparesis that typically develops during childhood. Lower-limb distal tendon reflexes are increased. Distal weakness, when present, is mild and disproportionate to the observed spasticity. Distal amyotrophy was found in all individuals older than age 13 years and also in one child age seven years reported by Proukakis et al [2004]. In the more severely affected, generally older, individuals, weakness of the small hand muscles was observed. Most individuals had mild weakness of the abductor pollicis brevis, abductor digiti minimi, and palmar and dorsal interossei. More proximal upper-limb strength is preserved. The most severely affected individuals had choreoathetoid movements (i.e., an irregular, constant succession of slow, spasmodic writhing with involuntary flexion, extension, pronation, and supination) of the fingers and hands, and sometimes the toes and feet. Difficulty with walking increased with age; affected individuals generally became wheelchair bound during the sixth to seventh decade of life.

Progressive spastic dysarthria is reported with brisk jaw jerk, often accompanied by slow, spastic tongue movements. Excessive drooling is commonly observed in childhood and persists into adulthood in the most severely affected individuals.

Microcephaly and macrocephaly have both been reported [Patel et al 2002, Proukakis et al 2004, Manzini et al 2010, Tawamie et al 2015, Butler et al 2016, Dardour et al 2017, Spiegel et al 2017].

Learning difficulties were reported in all but one affected individual of Amish descent. Most were able to complete eighth grade, the traditional end point of Amish education. In all but one individual, school performance was significantly worse than that of unaffected sibs. Most affected individuals had persistent cognitive deficits. Two individuals completed high school and worked for several years [Proukakis et al 2004].

Emotional lability and affective disorders including inappropriate euphoria and/or crying are common [Proukakis et al 2004, Tawamie et al 2015].

Skeletal abnormalities described in individuals with Troyer syndrome include the following:

- Short stature when compared to parents and/or sibs [Proukakis et al 2004]
- Overgrowth of the maxilla leading to overbite (5/6 individuals) [Manzini et al 2010]

- Small feet with *pes cavus* (17/21 individuals) [Proukakis et al 2004]
- "Hammer toes" in the most severely affected individuals [Proukakis et al 2004]
- Hyperextensible proximal interphalangeal joints of the fingers (8/21) [Proukakis et al 2004]
- Brachydactyly (5/6 individuals), clinodactyly, camptodactyly, and hypoplastic fifth middle phalanges [Manzini et al 2010]
- Mild knee valgus (4/21) [Proukakis et al 2004]
- Mild kyphoscoliosis has been reported but radiographic correlation was not available [Proukakis et al 2004]

Life expectancy is normal.

Neuroimaging. White-matter hyperintensities described include periventricular white-matter hyperintensity on T_2-weighted images reported in eight individuals [Proukakis et al 2004, Manzini et al 2010, Dardour et al 2017] and increased T_2/FLAIR signal within the ventrolateral thalami and posterior limb of the internal capsule reported in one individual [Butler et al 2016]. The white-matter abnormalities described are not specific to Troyer syndrome and can be present in other forms of hereditary spastic paraplegia.

Nerve conduction studies performed in two individuals who were not severely affected were normal in the right upper and lower limb. In one of these individuals, electromyography (EMG) was normal bilaterally except for a polyphasic potential in the medial head of the gastrocnemius on one side. In the other individual, EMG of the right upper and lower limb was normal [Proukakis et al 2004].

Genotype-Phenotype Correlations

No genotype-phenotype correlations have been observed.

Prevalence

The prevalence is unknown. A previous study documented 21 individuals with Troyer syndrome in a population of approximately 50,000 Amish [Patel et al 2002]. To date the c.1110delA variant has not been observed outside of the Old Order Amish population.

Troyer syndrome has now been reported in several additional individuals worldwide.

Genetically Related Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with germline pathogenic variants in *SPART*.

Differential Diagnosis

See Hereditary Spastic Paraplegia Overview for a review.

Troyer syndrome shares some features with ARSACS (*a*utosomal *r*ecessive *s*pastic *a*taxia of *C*harlevoix-*S*aguenay); however, nystagmus, abnormalities of ocular movement, and mitral valve prolapse are not features of Troyer syndrome.

Some Amish children/infants have been diagnosed with Silver-Russell syndrome due to low birth weight, relatively preserved head circumference, triangular face shape, and short stature; however, spastic paraplegia, a consistent feature of Troyer syndrome, is not seen in individuals with Silver-Russell syndrome.

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs of an individual diagnosed with Troyer syndrome, the evaluations summarized in this section (if not performed as part of the evaluation that led to the diagnosis) are recommended:

- Growth assessment including height, weight, and head circumference
- Consultation with a neurologist and examination to identify features of Troyer syndrome with attention to evidence of pyramidal and/or extrapyramidal movement disorders, distal amyotrophy, hyperreflexia, swallowing difficulties
- Developmental assessment with attention to gross motor and fine motor skills, as well as speech and language development, looking for possible dysarthria and tongue dyspraxia
- Psychological assessment, with attention to presence or absence of emotional lability
- Physical examination for skeletal abnormalities and x-ray examination for kyphoscoliosis as needed
- Consultation with a clinical geneticist and/or genetic counselor

Treatment of Manifestations

No specific treatment to prevent or reverse the neurologic degeneration in Troyer syndrome currently exists. Treatments are directed at reducing symptoms, maintaining mobility, and improving balance, strength, and agility. Individuals should be evaluated periodically (annually or as needed) by a neurologist, physiatrist, occupational therapist, and speech and language therapist to assess progression and develop treatment strategies to maximize walking ability and reduce symptoms.

- Daily physical therapy regimen directed toward maintaining and improving cardiovascular health, muscle strength, and gait and reducing spasticity. These recommendations are based on the experience of approximately 200 persons with hereditary spastic paraplegia, who nearly unanimously reported benefit from daily physical exercise [Fink 2003].
- Occupational therapy, assistive walking devices, and ankle-foot orthotics as required
- Speech and language therapy to improve/maintain speech and swallowing, and communication devices as required
- Medication to reduce drooling may be helpful.
- Medications to reduce muscle spasticity (e.g., Lioresal® [oral or intrathecal]). Dosages need to be individualized as some individuals have weakness with less spasticity (and thus do not benefit from large doses), while others have significant spasticity and require high doses. Tizanidine, dantrolene (see Agents/Circumstances to Avoid), and botulinum A and B toxin injections (Botox®, Dysport®, Xeomin®, or Myobloc®) have also been useful in reducing muscle spasticity.
- Medications to reduce urinary urgency (e.g., oxybutynin, solifenacin, mirabegron, intrabladder injections with Botox®)
- Antidepressants or mood stabilizers to manage emotional lability

See also Hereditary Spastic Paraplegia Overview.

Surveillance

The following are appropriate:

- Evaluation with a neurologist every six to 12 months (or as required depending on age and severity) to review symptoms, assess need for multidisciplinary input, and update medications
- Monitor for dysphagia to reduce risk of aspiration

- Psychiatric/psychological assessment as indicated
- Developmental assessment / cognitive testing as indicated depending on age and severity
- Annual assessment of orthopedic manifestations

Agents/Circumstances to Avoid

Dantrolene should be avoided in persons who are ambulatory as it may induce irreversible weakness, which can adversely interfere with overall mobility.

Evaluation of Relatives at Risk

See Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.

Therapies Under Investigation

Search ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe for information on clinical studies for a wide range of diseases and conditions.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, mode(s) of inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members; it is not meant to address all personal, cultural, or ethical issues that may arise or to substitute for consultation with a genetics professional. —ED.

Mode of Inheritance

Troyer syndrome is inherited in an autosomal recessive manner.

Risk to Family Members

Parents of a proband

- The parents of an affected individual are obligate heterozygotes (i.e., carriers of one *SPART* pathogenic variant).
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

Sibs of a proband

- At conception, the sibs of an affected individual have a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier.
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

Offspring of a proband. To date, individuals with Troyer syndrome are not known to reproduce [Patel & Crosby, personal observation].

Other family members. Each sib of the proband's parents is at 50% risk of being a carrier of a *SPART* pathogenic variant.

Carrier Detection

Carrier testing for at-risk relatives requires prior identification of the *SPART* pathogenic variants in the family.

Related Genetic Counseling Issues

Family planning

- The optimal time for determination of genetic risk, clarification of carrier status, and discussion of the availability of prenatal/preimplantation genetic testing is before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are carriers or are at risk of being carriers.

DNA banking. Because it is likely that testing methodology and our understanding of genes, pathogenic mechanisms, and diseases will improve in the future, consideration should be given to banking DNA from probands in whom a molecular diagnosis has not been confirmed (i.e., the causative pathogenic mechanism is unknown).

Prenatal Testing and Preimplantation Genetic Testing

Once the *SPART* pathogenic variants have been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic testing for Troyer syndrome are possible.

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing. While most centers would consider use of prenatal testing to be a personal decision, discussion of these issues may be helpful.

Resources

GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click here.

- **National Institute of Neurological Disorders and Stroke (NINDS)**
  Hereditary Spastic Paraplegia
- **Spastic Paraplegia Foundation, Inc.**
  Phone: 877-773-4483
  Email: information@sp-foundation.org
  sp-foundation.org

Molecular Genetics

Information in the Molecular Genetics and OMIM tables may differ from that elsewhere in the GeneReview: tables may contain more recent information. —ED.

Table A. Troyer Syndrome: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
SPART	13q13.3	Spartin	SPG20 database	SPART	SPART

Data are compiled from the following standard references: gene from HGNC; chromosome locus from OMIM; protein from UniProt. For a description of databases (Locus Specific, HGMD, ClinVar) to which links are provided, click here.

Table B. OMIM Entries for Troyer Syndrome (View All in OMIM)

275900	SPASTIC PARAPLEGIA 20, AUTOSOMAL RECESSIVE; SPG20

Table B. continued from previous page.

607111	SPARTIN; SPART

Molecular Pathogenesis

The pathogenic basis of Troyer syndrome is currently unclear.

Gene structure. *SPART* (formerly *SPG20*) resides within 731 kb and comprises nine exons. Multiple alternatively spliced variants, encoding the same protein, have been identified; the longest transcript is NM_015087.5. For a detailed summary of gene and protein information, see Table A, **Gene**.

Pathogenic variants. Four pathogenic *SPART* variants have been identified to date: c.1110delA in exon 4 in an extended Old Order Amish pedigree [Patel et al 2002], a recurrent homozygous 2-nucleotide deletion c.364_365delAT p.(Met122ValfsTer2) in Omani, Turkish, and Filipino families [Manzini et al 2010, Tawamie et al 2015, Butler et al 2016], a homozygous nonsense variant c.1369C>T (p.Arg457Ter) in a Moroccan family [Dardour et al 2017], and a homozygous 1-nucleotide substitution c.988A>G (p.Met330Val) in an Israeli-Arab child [Spiegel et al 2017].

Table 2. *SPART* Pathogenic Variants Discussed in This *GeneReview*

DNA Nucleotide Change	Predicted Protein Change (Alias [1])	Reference Sequences
c.988A>G	p.Met330Val	NM_015087.4 NP_055902.1
c.1369C>T	p.Arg457Ter	
c.1110delA	p.Lys370AsnfsTer30 (fs369-398Ter399)	
c.364_365delAT	p.Met122ValfsTer2 (M122V_C123Ter)	

Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.
GeneReviews follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.
1. Variant designation that does not conform to current naming conventions

Normal gene product. *SPART* (formerly *SPG20*) is widely expressed in adult and fetal human tissues. It encodes a 666-amino acid protein named spartin (spastic paraplegia autosomal recessive Troyer syndrome). Spartin possesses a MIT domain (contained within microtubule-interacting and trafficking molecules) [Ciccarelli et al 2003] as does spastin, which is encoded by *SPAST*, the most commonly mutated gene in hereditary spastic paraplegia, accounting for approximately 40% of autosomal dominant cases [Hazan et al 1999] (see Spastic Paraplegia Type 4). The identification of the same domain in spastin and spartin suggests related functionality of these proteins.

Spartin, a cytosolic and membrane-associated protein that interacts with EPS15, an endocytic and trafficking protein, may have a number of roles, including functioning at endosomes and in droplet formation [Bakowska et al 2005]. SPG20 associates with the surface of lipid droplets (LDs), regulating their size and number. SPG20 binds to another LD protein, TIP47; both proteins compete with an additional LD protein, adipophilin/adipocyte differentiation-related protein. Spartin may also be involved in endocytosis and vesicle trafficking [Bakowska et al 2005].

Abnormal gene product. Troyer syndrome is most likely caused by loss of function of spartin, as would be expected with an autosomal recessive disorder. A full explanation for the disease will require an understanding of the normal functions of spartin and the relevance of each function to axonal biology [Edwards et al 2009].

Chapter Notes

Author History

Emma Baple, MBBS, MRCPCH, PhD (2019-present)
Andrew Crosby, PhD (2004-present)
Gaurav Harlalka, MRes; University of London (2011-2019)
Heema Patel, PhD; University of London (2004-2019)

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