

Rapid introduction of a diagnostic service for
Brown-Vialetto-Van Laere syndrome (BVVLS)
and extension of the clinical phenotype

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BVLS - Summary

- First described by Brown in 1894, and later by Vialetto and Van Laere in 1936 and 1966 respectively
- Rare condition - only 58 cases reported in the last 100 years, although likely to be under-reported
- Neurodegenerative motor neuron disorder mainly affecting children but also older adolescents into adulthood
- *C20orf54* identified as causative gene in March 2010 (Green *et al* AJHG 86: 485-489)
- Service established at Guys DNA lab in July 2010

BVLS - Clinical symptoms

- Lower cranial nerve involvement - involved in facial expression, speech, taste, swallowing, head movement etc.
 - Facial and neck weakness or paralysis
 - Ptosis (droopy eyelids)
 - Limited/ absent speech
 - Dysphagia (difficulty swallowing)
- Respiratory compromise & diaphragmatic weakness leading to chest infections
- Muscle weakening & limb weakness (most patients wheelchair-bound)
- Sensorineural hearing loss (often the first sign)
- Normal mental function
- Aka Fazio-Londe syndrome (without deafness)

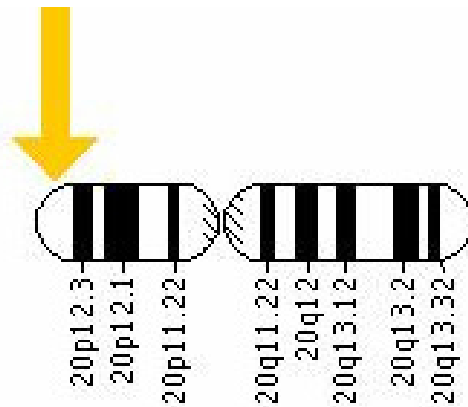
BVLS presentation & prognosis

- BVLS children often have a normal antenatal period, birth and infancy. Initial symptoms occur up to the third decade of life.
- Two main types of presentation:
 - Early onset, severe, rapid course (~6months to 5y/o)
 - Later onset, slowly progressive
- Poor prognosis:
 - Most patients survive ~5-10 years after onset of first symptoms.



Genetics

- Green *et al* identified *C20orf54* as causative gene in March 2010 - used autozygosity mapping (AJHG 2010)
- Autosomal recessive condition
- *C20orf54* is a small gene at 20p13, just 5 exons
- Exon 1 untranslated, exons 2-5 coding, sequenced in 6 fragments
- Highly conserved gene



C20orf54 protein

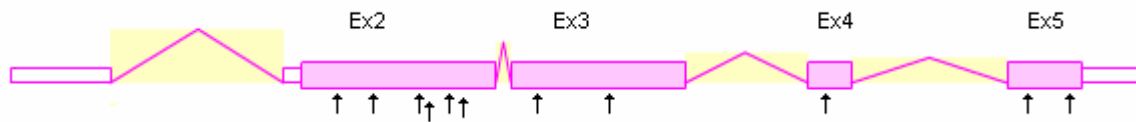
- 469 amino acids
- 11 transmembrane helices; therefore likely to be a transmembrane protein
- Likely function as a riboflavin transporter – rat ortholog of C20orf54 is a transporter of riboflavin in small intestine
 - Supplementation with riboflavin has demonstrated significant, but limited improvements in several BVVLS patients

Diagnostic service

- Introduction of *C20orf54* screening was expedited due to service requirements
 - 3 to 4 weeks to implementation
- Set up in July 2010 - offering diagnostic, carrier and prenatal testing by Sanger sequencing.
- Direct sequencing of the *C20orf54* gene in 6 fragments (4 exons)
- So far:
 - Screened 27 diagnostic samples
 - Carrier tested 20 parents
 - Performed four prenatals

Mutation screening results

- 11 different mutations/ variants detected:
 - 1 stop mutation
 - 2 frameshifts
 - 8 missense changes



- Mutations spread across gene, although the p.Tyr213X mutation may be more common:
 - Found in four patients: 1 from Germany, 2 siblings of N European origin & 1 from USA
 - Also reported in a Dutch patient
- Fully inherited - no *de novo* changes detected so far
 - Some sporadic cases reported in literature
- Possibility of the involvement of other genes responsible for the condition.
- At least 3/11 of diagnostic BVVLS positives previously tested for SMARD1. Also one patient in the Green *et al* paper previously tested negative for SMARD1.
 - ?clinical overlap of BVVLS and SMARD1

BVLS vs SMARD1 patients

	BVLS	SMARD1
Onset	Infancy to young adults	From birth; few cases of juvenile onset reported
Presenting signs	Sensorineural deafness, limb weakness, respiratory compromise	Respiratory distress, hypotonia, pneumonia
Deafness	Yes, may precede neurological picture	No
Diaphragmatic paralysis & respiratory distress	Yes - ventilatory support required in most cases	Yes – ventilatory support required in most cases. Sudden & rapid progression
Muscle weakness	Yes – facial, upper and lower limbs	Yes – mainly lower limbs and distal muscles
Course	Progressive but fluctuating picture	Invariably progressive
Disease duration	Months to decades	Months to years depending on support
Inheritance	Autosomal recessive	Autosomal recessive

BVLS testing in SMARD1 negative cohort

- Identified and reversibly anonymised 95 SMARD1 negative patients
- Performed full screen for mutations in *C20orf54*:
 - Found 2 positives
 - Both from consanguineous families – hom frameshift and hom missense
- A diagnosis of BVLS may be considered in some SMARD1-negative patients

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