Loeys Dietz Syndrome

Introduction

Loeys-Dietz syndrome (LDS) is an aortic aneurysm syndrome characterised by widely spaced eyes (hypertelorism), bifid uvula and/or cleft palate and generalised arterial tortuosity with ascending aortic aneurysm and dissection. Affected patients have a high risk of aortic dissection or rupture at an early age and at aortic diameters that ordinarily would not be predictive of these events. LDS shows autosomal dominant inheritance and variable clinical expression. Approximately 25% of individuals diagnosed with LDS have an affected parent, with the remaining 75% due to de novo pathogenic variants. LDS is caused by pathogenic variants in TGFBR1 and TGFBR2.

Both proteins are transmembrane serine/threonine receptor kinases. TGFBR1 contains 9 exons and spans approximately 53 kb. TGFBR2 contains 8 exons in the longest transcript, including the alternatively spliced exon 1A, and spans approximately 91 kb. Pathogenic variants throughout the coding region of both genes have been reported including frame shift, nonsense, missense and splice site pathogenic variants as well as small insertions or deletions. Most pathogenic variants are missense variants in or immediately flanking the serine-threonine kinase domains of either receptor. Analysis is by sequencing of all coding exons of both genes and will detect >95% of pathogenic variants in individuals with typical findings of LDS.

Referrals

- New referrals should fulfill the UKGTN testing criteria.
- Mutation testing can be offered to the relatives of LDS patients once a pathogenic variant has been identified.

Prenatal testing

Prenatal testing is available for families in whom pathogenic variants have been identified or in whom appropriate family studies have been undertaken; please contact the laboratory to discuss.

Service offered

Screening of the entire coding regions and intron-exon boundaries of TGFBR1 & 2 for diagnostic tests.

Testing for previously identified familial pathogenic variants is available to other family members.

Technical

Analysis is by next generation sequencing (Agilent SureSelect and Illumina NextSeq). A minimum coverage of 30 reads is required to call a variant. In-house validation attributes a minimum sensitivity of 97.5% (with 95% confidence) for regions covered >30x. This assay is not currently validated to detect large deletions / duplications. All clinically relevant variants are confirmed by Sanger sequence analysis. Known benign polymorphisms and sequence variants which are unlikely to be pathogenic are not reported.

Familial testing is carried out by direct sequencing analysis.

Target reporting time

The target reporting time for both genes is 8 weeks. The target turnaround time for familial variants (incl. predictive tests) is 4 weeks. Please contact the laboratory for urgent cases.