### Dense Deposit Disease (DDD) and C3 Glomerulonephritis (C3GN)

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<tr>
<th>C3</th>
<th>CFB</th>
<th>CFH</th>
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<td>CFHR5</td>
<td>CFI</td>
<td>MCP</td>
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**Description:**

C3 Glomerulopathy (C3G) defines a group of renal diseases characterized by glomerular accumulation of complement C3 with scant or absent accumulation of immunoglobulins as assessed by immunofluorescence, indicative of activation of the alternative complement pathway (AP). C3G is comprised primarily of two distinct entities, dense deposit disease (DDD) and C3 glomerulonephritis (C3GN), which may be distinguished by electron microscopy. Dense deposit disease is characterized by accumulation of intramembranous sausage-shaped or ribbon-shaped electron-dense deposits. C3GN is a more heterogeneous group of disorders, characterized by isolated or predominant C3 staining on immunofluorescence with ultrastructural evidence of mesangial, subepithelial, or subendothelial electron-dense deposits (Xiao et al., 2014).

Clinical presentations of these disorders may include asymptomatic hematuria and proteinuria, nephrotic syndrome, and acute glomerulonephritis. Outside of renal manifestations, patients with DDD may also ocular drusen resulting from retinal deposits and acquired partial lipodystrophy.

Pivotal to the underlying pathogenesis of C3G is dysregulation of the AP C3 convertase C3bBb occurring primarily in the fluid phase, leading to hypocomplementemia from C3 consumption. Such dysregulation occurring at the cell surface instead leads to endothelial cell injury and thrombotic microangiopathy as seen in atypical hemolytic uremic syndrome (aHUS). Dysregulation of the AP C3 convertase is due to acquired factors such as C3 Nephritic Factor (~80% of patients with DDD and ~50% of patients with C3GN) or monoclonal gammapathy, and genetic factors such as mutations in complement regulatory proteins (Zhang et al. 2012). As mutations in these regulatory proteins can be identified in either C3G or aHUS, other genetic and environmental factors likely contribute to the predominance of one or the other clinical presentations.

Approximately 50% of patients with DDD progress to end-stage renal disease within 10 years of diagnosis (Smith et al. 2011), whereas the progression to ESRD appears to be slower in C3GN (Xiao et al. 2014). Following renal transplantation, histological recurrence of DDD in the renal allograft is nearly universal, with 50% graft failure in 5 years. Recurrence is also seen in ~70% of patients transplanted with C3GN with graft loss in ~50% of patients due to recurrence.

Immunosuppressive medications and/or plasma exchange may be effective in some patients with DDD and C3GN, particularly if an acquired form of complement dysregulation (i.e. C3NeF) is present. Complement-directed therapy with eculizumab, a humanized monoclonal antibody targeted against the complement protein C5, has been shown to be effective in some patients with DDD and C3GN, particularly if activation of the terminal complement pathway was present (Bomback et al., 2012).

**Indications:**

**Dense deposit diseases/C3 Glomerulonephritis Panel by NGS:**
- Diagnostic testing in patients with dense deposit disease (DDD) or C3 glomerulonephritis (C3GN)
- Presymptomatic diagnosis for at-risk individuals with a family history of dense deposit disease (DDD) or C3 glomerulonephritis (C3GN).

**Mutation Specific Analysis:**
- Presymptomatic testing of at-risk siblings for medical management
- Prenatal diagnosis of an at-risk fetus, after confirmation of mutation in the parent(s) (by prior arrangement only).

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**Specimen:**
Dense deposit diseases/C3 Glomerulonephritis panel by NGS: At least 5 mLs whole blood in a lavender top (EDTA) tube.

**Mutation Specific Analysis:** At least 3 mLs whole blood in a lavender top (EDTA) tube. Please indicate previously identified mutation on the requisition. Label tubes with patient’s name, birth date, and date of collection.

**Testing Methodology:**
This test is performed by enrichment of the exons, flanking intronic and un-translated regions (5’ and 3’) of the genes specified above using microdroplet PCR technology followed by next-generation sequencing with > 40 fold coverage at every target base. All pathogenic and novel variants, as well as variants of unknown (indeterminate) significance, as determined bioinformatically, are confirmed by Sanger sequencing.

**Gene Specific Sequencing/Mutation Specific Analysis:** Sanger sequencing following PCR amplification of the specified coding and exon/intron boundaries of the specified gene.

**Sensitivity:**
**Clinical Sensitivity:** Mutations in CFH, CFI, or MCP are identified in approximately 17% of patients with DDD and 13% of patients with C3GN (Servais et al. 2012) and may be identified in CFB, C3, and CFHR5 as well (Pickering et al. 2013).

**Analytical Sensitivity:** The sensitivity of DNA sequencing is over 99% for the detection of nucleotide base changes, small deletions and insertions in the regions analyzed.

**Limitations:** Mutations in regulatory regions or other untranslated regions are not detected by this test. Large deletions involving entire single exons or multiple exons, large insertions and other complex genetic events will not be identified using this test methodology. Rare primer site variants may lead to erroneous results.

**Turn-Around Time:** 30 days

**CPT Codes:**
- Dense deposit diseases/C3 Glomerulonephritis panel: 81479x6
- Mutation specific analysis: 81479

Please call 1-866-450-4198 for current pricing, insurance preauthorization or with any billing questions.

**Results:**
Each test report includes a detailed interpretation of the genetic findings, the clinical significance of the result, and specific recommendations for the clinical management and additional testing, if warranted. Results will be reported to the referring physician or health care provider as specified on the test requisition form.

**Shipping Instructions:**
Please enclose test requisition with sample. All information must be completed before sample can be processed.

Place samples in styrofoam mailer and ship at room temperature by overnight Federal Express to arrive Monday through Friday.

**Ship to:**
Cytogenetics and Molecular Genetics Laboratories
3333 Burnet Avenue NRB 1042
Cincinnati, OH 45229
513-636-4474

**References:**


