# The University of Chicago Genetic Services Laboratories

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## *CDKN1C* Mutation Analysis

### Clinical Features:

Beckwith-Wiedmann syndrome [BWS, MIM# 130650] is an overgrowth syndrome, involving predisposition to tumor development. The clinical presentation is highly variable and includes macrosomia, macroglossia, visceromegaly, embyronal tumors, omphalocele, neonatal hypoglycemia, ear creases/pits, adrenocortical cytomegaly and renal anomalies (1).

IMAGe syndrome [MIM#614732] is an acronym: I = intrauterine growth retardation; M = metaphyseal dysplasia; A = adrenal hypoplasia congenital; Ge = genital anomalies. Patients can present shortly after birth with severe adrenal insufficiency, which can be life threatening. Other reported features include hypercalciuria and/or hypercalcemia, craniosynostosis, cleft palate and scoliosis (2).

### Molecular Genetics:

Mutations of the *CDKN1C* [OMIM #171833] gene have been identified in patients with BWS. Lam et al, 1999 identified *CDKN1C* mutations in 43% of familial cases and 4% of sporadic cases of BWS (3). Missense and nonsense mutations have been identified in BWS-associated *CDKN1C* and are typically localized to the cyclin-dependent kinase binding domain and results in protein loss-of-function, over proliferation and predisposition to cancer.

Mutations of the *CDKN1C* gene have also been recently identified in patients with IMAGe syndrome. Arboleda et al, 2012 identified *CDKN1C* mutations in two familial and four unrelated patients with IMAGe syndrome (4).To date, only missense mutations have been identified in IMAGe-associated *CDKN1C* and are localized to the PCNA binding domain resulting a gain of function in excess inhibition of growth and differentiation (4).

### Inheritance:

The *CDKN1C* gene is paternally imprinted, with preferential expression of the maternal allele. Several instances of maternal transmission of a *CDKN1C* mutation from a clinically unaffected mother to her affected offspring have been reported. One instance of paternal transmission of a *CDKN1C* mutation from a clinically unaffected father has been reported (5). Recurrence risk can be as high as 50% depending on the carrier status of the parent.

### Test Methods:

We offer full gene sequencing of all coding exons and intron/exon boundaries of *CDKN1C* by direct sequencing of amplification products in both the forward and reverse directions.

Our CNV detection algorithm was developed and its performance determined for the sole purpose of identifying deletions and duplications within the coding region of the gene(s) tested. Partial exonic copy number changes and rearrangements of less than 400 bp may not be detected by this methodology. Regions of high homology and repetitive regions may not be analyzed. This methodology will not detect low level mosaicism, balanced translocations, inversions, or point mutations that may be responsible for the clinical phenotype. The sensitivity of our deletion/duplication assay may be reduced when DNA extracted by an outside laboratory is provided.

*CDKN1C* mutation analysis

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| Sample specifications: | 3 to 10cc of blood in a purple top (EDTA) tube |
| Cost: | $840 |
| CPT codes: | 81404 |
| Turn-around time: | 4 weeks |

## Results:

Results, along with an interpretive report, will be faxed to the referring physician. Additional reports will be provided as requested. All abnormal results will be reported by telephone.

## References:


1. Weksberg R, Shuman C, Smith AC. Beckwith-Wiedemann syndrome. Am J Med Genet C Semin Med Genet 2005: 137C: 12-23.
2. Balasubramanian M, Sprigg A, Johnson DS. IMAGe syndrome: Case report with a previously unreported feature and review of published literature. Am J Med Genet A 2010: 152A: 3138-3142.
3. Lam WW, Hatada I, Ohishi S et al. Analysis of germline CDKN1C (p57KIP2) mutations in familial and sporadic Beckwith-Wiedemann syndrome (BWS) provides a novel genotype-phenotype correlation. J Med Genet 1999: 36: 518-523.
4. Arboleda VA, Lee H, Parnaik R et al. Mutations in the PCNA-binding domain of CDKN1C cause IMAGe syndrome. Nat Genet 2012: 44: 788-792.
5. Lee MP, DeBaun M, Randhawa G et al. Low frequency of p57KIP2 mutation in Beckwith-Wiedemann syndrome. Am J Hum Genet 1997: 61: 304-309.


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