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### Clinical validation and diagnostic rate/outcomes of a dual molecular diagnostic assay for myotonic dystrophy 1.

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# Clinical validation and diagnostic rate/outcomes of a dual molecular diagnostic assay for myotonic dystrophy 1

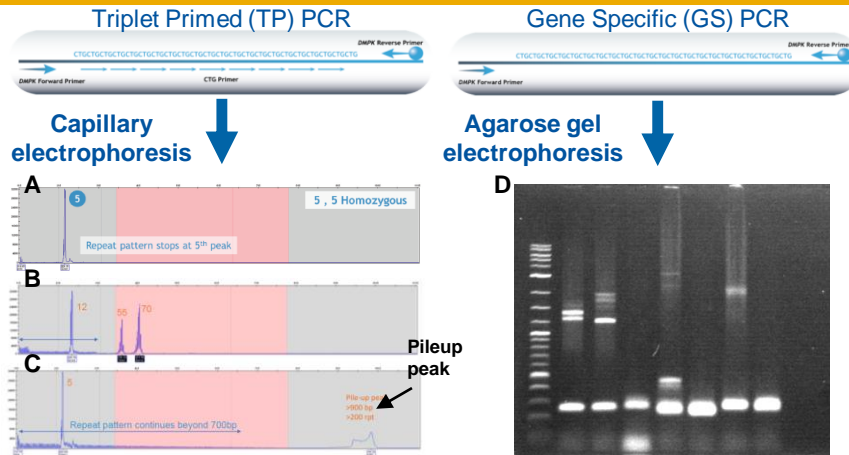
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## Background

Myotonic dystrophy type 1 (DM1) is caused by a (CTG)<sub>n</sub> repeat expansion in the 3' UTR of DMPK and is an important and often overlooked consideration in the work up of a hypotonic infant. (CTG)<sub>n</sub> repeats are refractory to detection by short read sequencing and therefore, require other specialized methods for accurate quantification including PCR and Southern blot (SB) analysis. Current laboratory-developed PCR tests are limited to amplification of >100 repeats and require multiple reactions for either expansion detection or accurate sizing due to amplification dropouts. Furthermore, SB is labor-intensive, expensive, and has a significantly increased turnaround time. Here, we describe the clinical validation and implementation of a new commercially available PCR assay that overcomes these significant hurdles (AmplideX PCR/CE DMPK, Asuragen).

## Methods: workflow



**Figure 1:** Method workflow. Samples undergo TP PCR and resolved using capillary electrophoresis. A maximum of 200 repeats can be detected and zygosity can be resolved using this method. In addition, detection of mosaicism can be clearly identified. However, samples with greater than 200 repeats can be resolved by gene specific PCR and agarose gel electrophoresis.

## Results: Validation summary

A validation set of 23 samples was tested. Samples were selected to provide multiple representatives in each numerical category throughout the dynamic range which included the normal (5-34 repeats), premutation (35-49 repeats), and various disease ranges (>50 repeats). We observed 100% concordance between our results for this sample set and previously reported results with 100% sensitivity, specificity, accuracy, and precision. In addition, we were able to clearly resolve zygosity in all samples. Mosaicism of at least 10% was detectable.

## Results: Clinical results

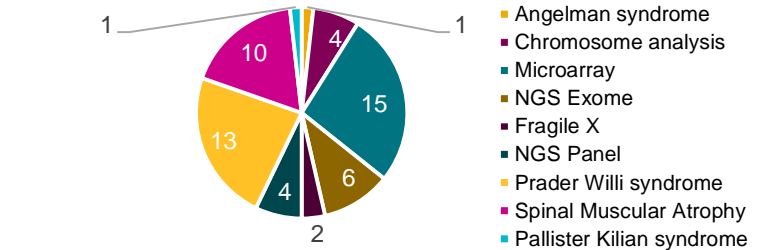
**Table 1:** Since implementing this test clinically, 28 individuals have been tested.

Sample	n	Percent
Positive	8	28.6 %
Negative	20	71.4 %

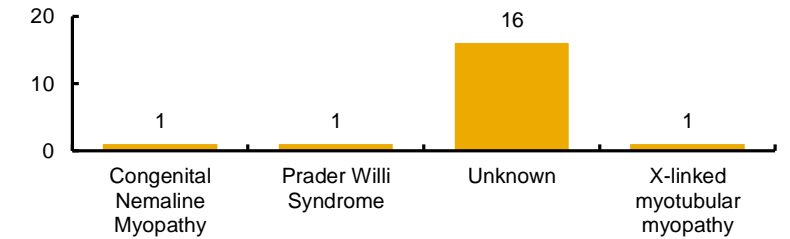
Proband	Alleles	Age (years)	Presenting feature
1	11, 594-928	0.5	Congenital hypotonia
2	11, 920	3	Congenital hypotonia
4	11, ~500	1.3	Developmental delay
6	13, ~660	15	ID and muscular dystrophy
9	11, 600-900	19	Hypotonia, craniofacial abnormalities
14	13, 230, ~ 150-280	0.75	Hip dysplasia
Mother of proband 4	5, 18, 60, ~428-594	28	Handgrip myotonia, bradycardia, poor vision
Mother of proband 1	20, ~100-230	38	"Trigger finger", IBS

**Table 2:** In 6/25 patients (24% of total), we detected expanded alleles between 500-900 repeats and reported a diagnosis of DM1. Two of three parents who underwent carrier testing following the diagnosis of an affected child were found to have somatic mosaicism. In both cases, the expansion was maternally-inherited. Interestingly, all mothers tested for the repeat expansion showed signs of DM1, but none were previously diagnosed with the disease.

## Results: Additional testing



**Figure 2:** Most patients (20/25 patients) underwent additional testing



**Figure 3:** Diagnosis in patients negative for the expansion

## Conclusions

1. We validated and implemented a faster, accurate, and cost-effective approach to diagnosis DM1 molecular. The workflow of the test is streamlined and can be performed within 7 hours with a total hands-on time of 1 hour for each workflow.
2. Our laboratory tested 25 patients with clinical features suggesting DM1; 6 were positive for an expanded allele. In addition, we identified mosaicism in two parental samples. The high diagnostic rate of DM1 indicates a potentially large number of undiagnosed patients.
3. Our results suggests that DM1 testing should be ordered early on in infant with hypotonia, potentially even prior to NGS and CGH-array. As such, we offer DM1 along with PWS and SMA as a Congenital Hypotonia panel.
4. Considering the high recurrence of DM1, establishing the diagnosis is essential to provide appropriate genetic counseling to the family.