The ATP1A3-D801N variant is associated with life-threatening paradoxical shortening of the corrected QT interval during periods of bradycardia and nodal dysfunction in humans

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BACKGROUND

- Alternating hemiplegia of childhood (AHC) is associated with short QTc and sinus node dysfunction among patients with ATP1A3-D801N[1-4].
- There is risk of ventricular fibrillation following bradycardia[1], but the mechanism is unknown.

STUDY OBJECTIVE

To investigate how QT and QTc change with heart rate (HR) in AHC, specifically ATP1A3-D801N.

METHODS

- DUHS IRB-approved with consent waiver.
- **Cohort**: Healthy, ATP1A3-D801N, ATP1A3 non-D801N, *ATP1A3* loss of function (LOF), and *ATP1A3* genotype negative
- Linear regression analysis of available Holter recordings.
- International cohort for analysis of sinus node dysfunction.

DISCLOSURES

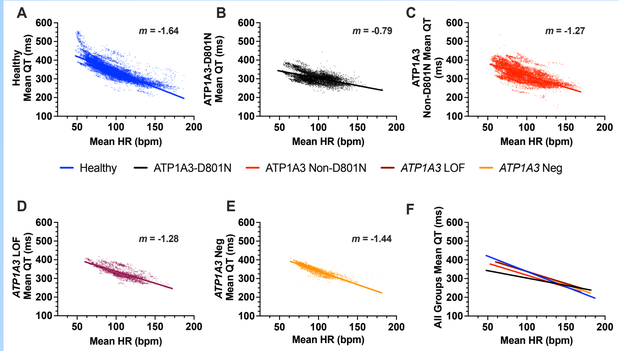
MAM has intellectual property interest in gene therapy for *ATP1A3*-related disease pending patent application.

RESULTS

Table 1. Cohort Demographics.

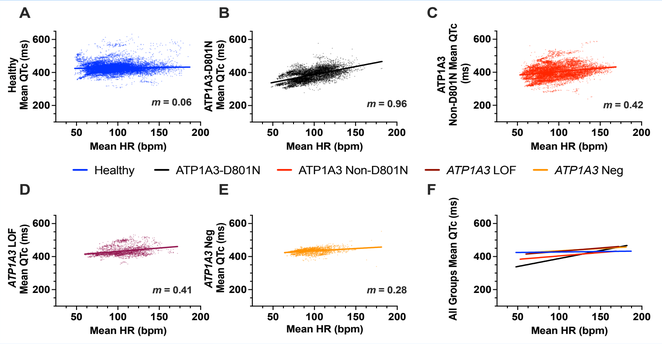
	Healthy	ATP1A3-Related Phenotype	ATP1A3-D801N	ATP1A3 Non-D801N	ATP1A3 LOF	ATP1A3 Neg	*P* value
Number of Individuals	36	44	9	25	4	6	
Number of Holter Recordings	57	81	25	38	9	9	
Sex (% F)	52.78	52.27	55.56	52.00	50.00	50.00	>0.9999
Mean Age at First Holter (SD)	9.84 (7.94)	8.04 (8.50)	4.28 (4.93)	9.78 (10.26)	3.23 (1.91)	9.67 (3.50)	0.16

Figure 1. ATP1A3-D801N is associated with blunted prolongation of QT at slower HR compared to healthy.



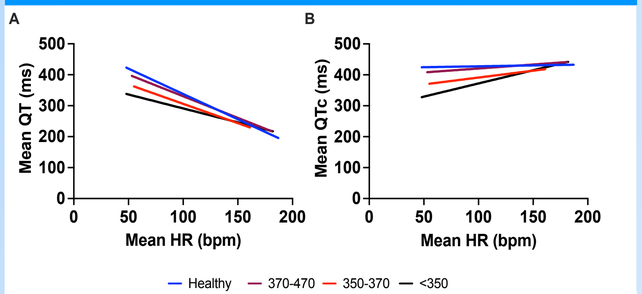
Linear regression analysis of mean HR versus mean QT. *m* represents slope of the linear regression line of fit. **A.** Healthy. **B.** ATP1A3-D801N. **C.** ATP1A3 Non-D801N. **D.** *ATP1A3* LOF. **E.** *ATP1A3* Negative. **F.** Lines of fit for all groups.

Figure 2. ATP1A3-D801N is associated with increased shortening of QTc at lower HR compared to healthy.



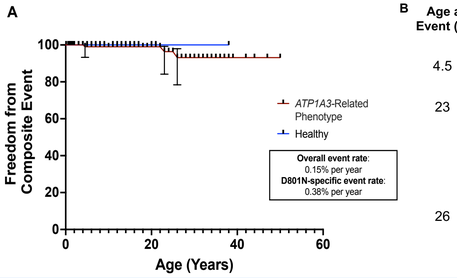
Linear regressions for mean HR versus mean QTc. *m* represents slope of the linear regression line of fit. **A.** Healthy. **B.** ATP1A3-D801N. **C.** ATP1A3 Non-D801N. **D.** *ATP1A3* LOF. **E.** *ATP1A3* Negative. **F.** Lines of fit for all groups.

Figure 3. Short baseline QTc is associated with impairment of QT/QTc dynamics.



QT/QTc dynamics grouped by baseline QTc on ECG. **A.** Mean HR versus mean QT. **B.** Mean HR versus mean QTc.

Figure 4. ATP1A3-D801N is associated with sinus node dysfunction.



B

Age at Event (y)	Genotype	Composite Event
4.5	ATP1A3-D801N	Sinus pauses >4, cardiac arrest
23	ATP1A3-S137F	Pacemaker for sinus arrest
26	ATP1A3-D801N	Sinus pauses >4, ICD for sinus node dysfunction, 3rd degree AV block, syncope

A. Kaplan-Meier analysis of freedom from composite events versus age in *ATP1A3*-related phenotypes compared to healthy. **B.** Characteristics of patients with composite events.

SUMMARY OF RESULTS

- Individuals with ATP1A3-D801N show a paradoxical shortening of QT and QTc at lower HR.
- Baseline QTc <350ms on ECG is associated with impaired QT and QTc dynamics.
- There is a greater rate of significant sinus node dysfunction in ATP1A3-D801N than all other genotypes combined.

CONCLUSIONS

Short baseline QTc, combined with abnormal QTc dynamics, could increase the risk of arrhythmia and sudden cardiac death during bradycardia in individuals with ATP1A3-D801N.

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REFERENCES

1. Moya-Mendez, M.E., et al. ATP1A3-Encoded Sodium-Potassium ATPase Subunit Alpha 3 D801N Variant Is Associated With Shortened QT Interval and Predisposition to Ventricular Fibrillation Preceded by Bradycardia. *Journal of the American Heart Association*. 2021;10:e019887. doi:10.1161/JAHA.120.019887
2. Jaffer F, Avbersek A, Vavassori R, Fons C, Campistol J, Stagnaro M, De Grandis E, Veneselli E, Rosewich H, Gianotta M, et al. Faulty cardiac repolarization reserve in alternating hemiplegia of childhood broadens the phenotype. *Brain*. 2015;138:2859-2874. doi: 10.1093/brain/awv243
3. Balestrini S, Mikati MA, Alvarez-Garcia-Roves R, Carboni M, Hunanyan AS, Kherallah B, McLean M, Prange L, De Grandis E, Gagliardi A, et al. Cardiac phenotype in ATP1A3-related syndromes: A multicenter cohort study. *Neurology*. 2020;95:e2866-e2879. doi: 10.1212/WNL.0000000000010794
4. Novy J, McWilliams E, Sisodiya SM. Asystole in alternating hemiplegia with de novo ATP1A3 mutation. *European Journal of Medical Genetics*. 2014;57:37-39. https://doi.org/10.1016/j.ejmg.2013.11.003