Finding suitable clinical endpoints for a potential treatment of a rare genetic disease: The case of ARID1B

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Introduction

Treatment of patients with intellectual disability (ID) is challenging. Effective treatments are not available, conducting clinical trials with potential treatments for ID is difficult and ID trials rely on subjective endpoints like IQ measurement and questionnaires, which are unsuitable for early drug research. As a result most clinical trials in ID have failed to demonstrate significant treatment effects despite promising preclinical data. In the case of ARID1B-related intellectual disability, preclinical data shows potential beneficial effects of clonazepam (Jung 2017). However, for a subsequent clinical trial, appropriate endpoints have to be established first.

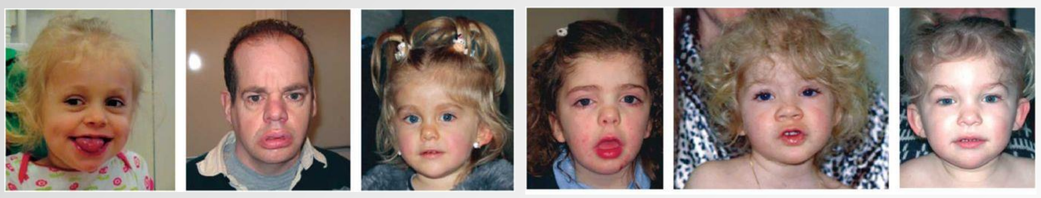

Figure 1. Patients with ARID!B-related ID (Source: Santen 2012)

Aims

The aim of this study was to assess the suitability of several non-invasive clinical endpoints for all age groups ARID1B-related intellectual disability.

Criteria for an ideal biomarker:
- Sensitive to CNS effects of pharmacological interventions
- Feasible to perform multiple times in this population
- Differentiate between control subjects and patients
- Correlate with known measures of disease-activity

Methodology

We performed a study with 12 ARID1B subjects and 12 healthy age-matched controls (range 2 - 31 years). Tests were performed 1-2 times on two separate study days, table 1. A mixed model analysis assessed differences between ARID1B and healthy subjects. Mean test outcomes were correlated with Aberrant Behavior Checklist (ABC) questionnaire and IQ. A Withings® Steel HR smartwatch was worn between the study days.

Table 1. Rationale for selected tests

	Test	CNS domain	Corresponding ARID1B symptom
Memory	Animal fluency test	Fluency and memory	Intellectual disability
	VVLT	Memory	Intellectual disability
	Day-Night test	Memory and inhibition	Impulsiveness and ID
Visuo-motor	Adaptive tracking	Coordination and attention	Short attention span
	Finger tapping	Motor activation and fluency	Lethargy
	Body sway	Balance and attention	Hyperactivity
Eye movement	Smooth pursuit	Oculomotor function	Candidate
	Saccadic eye movement	Sedation	drug effect
EEG	Resting EEG	General CNS activity	Hypothesized abnormal neuronal organization
	Passive oddball	Auditory processing	
	Active oddball	Auditory processing	
	VEP	Visual processing	
	ASSR	Auditory processing	
Trial @home	Physical activity	General daily activity	Hyperactivity / lethargy
	Sleep parameters	Sleep	Insomnia
	Heart rate	Arousal and activity	Hyperactivity

Results

In the ARID1B subjects:
- VVLT and active oddball could not be performed adequately.
- EEG: high variability and execution considered as very trying
- Acceptable variability for visuo-motor and memory tests.
- Differentiation between ARID1B subjects and controls for adaptive tracking, finger tapping, smooth pursuit eye movements, body sway animal fluency test, and visual evoked potentials.
- Moderate correlations for animal fluency test and historic IQ and Aberrant Behavior Score (ABC) subscales and visuomotor tests.
- Physical activity pattern in ARID1B showed distinct difference.

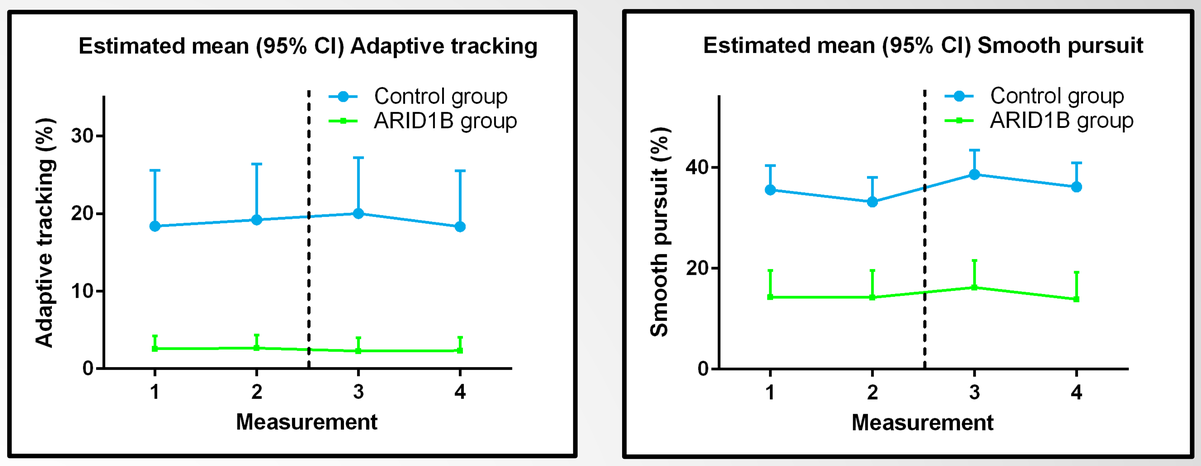

Figure 1. LSM for adaptive tracking (left) and smooth pursuit (right) tests

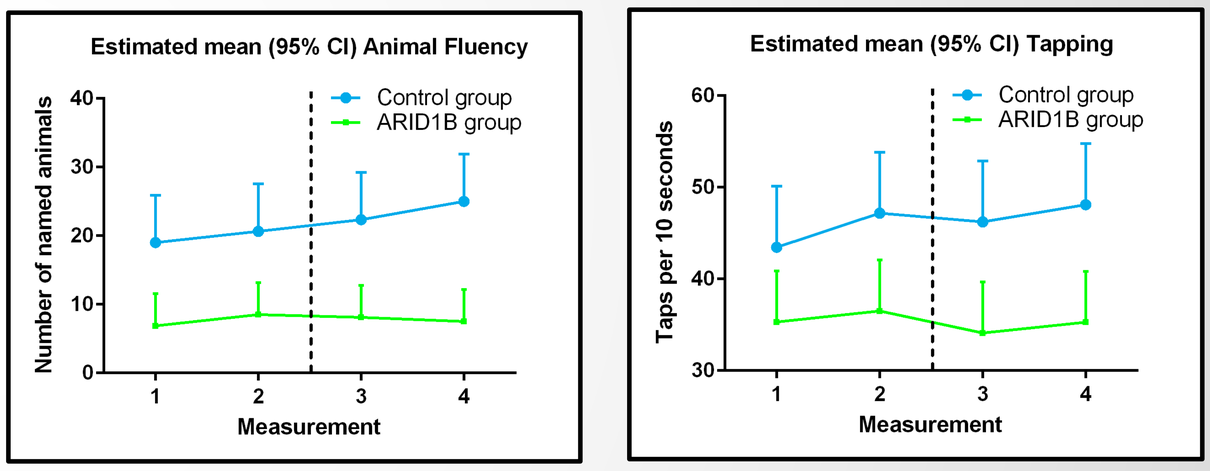

Figure 2. LSM for animal fluency (left) and finger tapping (right) tests

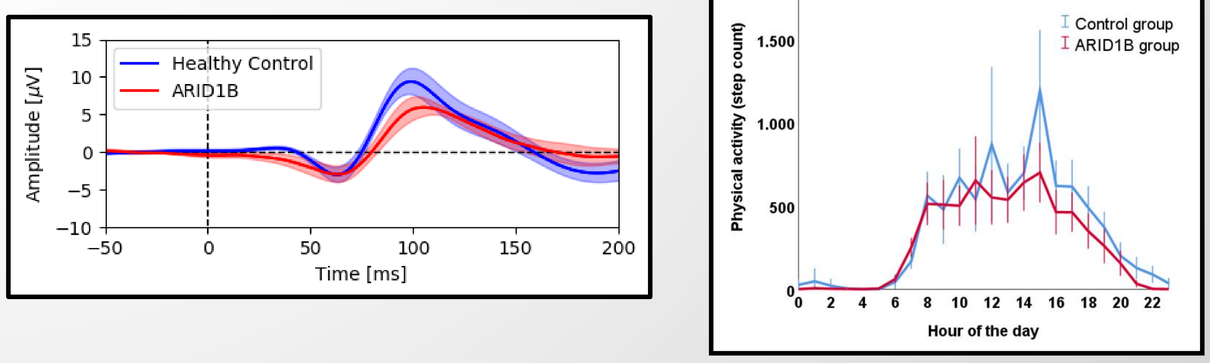

Figure 4. ERP graph of VEP (left) and average physical activity / hour (right)

Conclusion

- We have identified finger tapping, adaptive tracking, smooth pursuit eye movements and the animal fluency as suitable clinical endpoints for early phase drug trials in ARID1B-related intellectual disability.
- These candidate endpoints will be evaluated in a study investigating the effects of clonazepam in this population.
- EEG tests were considered too invasive despite its ability to differentiate between ARID1B- patients and healthy controls

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