

FAMILIAL AGGREGATION OF RESPONSE TO CGRP MONOCLONAL ANTIBODIES IN MIGRAINE: PRELIMINARY CLINICAL EVIDENCE OF INHERITED TREATMENT SUSCEPTIBILITY

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Background. Drugs targeting the calcitonin gene-related peptide (CGRP-mAbs) have demonstrated efficacy in randomized clinical trials and real-world studies. Nevertheless, approximately one-third of patients fail to achieve a clinically meaningful response, suggesting substantial biological heterogeneity in the contribution of CGRP-dependent mechanisms to migraine pathophysiology. Given the well-established familial aggregation of migraine, we investigated the familial aggregation of therapeutic response to CGRP-mAbs, hypothesizing that responsiveness to CGRP-targeted therapies may aggregate within families, putatively reflecting shared inherited biological determinants.

Methods. This is a prospective, single-center observational study including patients with migraine and at least one first-degree relative also treated with CGRP-mAbs. The primary outcome was familial aggregation of treatment response, evaluated as the change in monthly headache days from baseline to 6th month. A linear mixed-effects model including family as a random intercept was used to partition treatment-response variability into between-family and within-family components, with the intraclass correlation coefficient (ICC) quantifying familial clustering after adjustment for age, sex, baseline headache frequency, migraine subtype, medication-overuse headache, and previous preventive treatment failures. As a secondary analysis, response was dichotomized as a ≥50% reduction in monthly headache days. Families were classified as concordant responders, concordant non-responders, or discordant, and the observed concordance was compared with that expected under independent treatment responses.

Results. Fifty patients from 23 families completed the six-month follow-up. After adjustment for demographic and clinical covariates, family membership accounted for a substantial proportion of treatment-response variability (ICC = 0.57), indicating that more than half of the residual variability was attributable to between-family differences. Twenty of the 23 families (87.0%) showed concordant treatment response, including 16 concordant responder families and four concordant non-responder families, whereas only three families were discordant. The observed concordance markedly exceeded the 65.7% expected under the assumption of independent treatment responses.

Conclusions. Treatment response to CGRP-mAbs shows a high degree of intrafamilial concordance that remains largely independent of established clinical predictors, suggesting that shared familial determinants contribute to treatment response. The marked familial aggregation observed in our cohort provides a strong rationale for pharmacogenetic studies aimed at identifying the molecular determinants of treatment response and advancing precision medicine in migraine prevention.