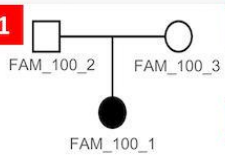
seqr Summary Data Reports Search project, family, gene name, etc. Logged in as **Broad Analyst** Log out

Family Variant Search

Project>> Neuromuscular Cohort>> Family: FAM_100

1



2

Family Description:
Isolated case of a female with LGMD

Analysis Status:

3

Solved, known gene for phenotype

Assigned Analyst Broad Analyst
Analysed By analyst@broadinstitute.org on 08/23/2021

Case Notes Add Note + Sanger confirmed, proceed to reporting.
Analysis Notes Add Note + Completed standard de novo/dominant and recessive searches
Matchmaker Notes Add Note + Not submitted
Coded Phenotype:
limb-girdle muscular dystrophy

Post-discovery OMIM #
253600

7

Variant Search
Add Manual Variant +
Add Manual SV +
MatchMaker Exchange

FAM_100_1

Added 11/05/2020

4

Age:
24

Age of Onset:
Childhood onset

Individual Notes
Consanguinity:
Other Affected Relatives:
Expected Mode of Inheritance:
Autosomal dominant inheritance, Autosomal recessive inheritance

Assisted Reproduction:

Maternal Ancestry: French

Paternal Ancestry: Italian

Imputed Population:
European (non-Finnish)

SV QC Flags:
Raw Calls: >100

Features: Present
Limbs: Limb-girdle muscular dystrophy

Pre-discovery OMIM disorders:
253600

Previously Tested Genes:
(None)

Candidate Genes: Genes associated with LGMD

8

- WES - SV LOADED 5/26/2021
- WES LOADED 5/7/2020
- WES LOADED 10/23/2017

FAM_100_2

Added 11/05/2020

5

Age:
65

Individual Notes
Maternal Ancestry: Italian

Paternal Ancestry: Italian

Imputed Population:
European (non-Finnish)

Features: Unaffected

- WES LOADED 5/26/2021
- WES - SV LOADED 5/25/2021
- WES LOADED 12/15/2020

FAM_100_3

Added 11/05/2020

6

Age:
60

Individual Notes
Maternal Ancestry: French

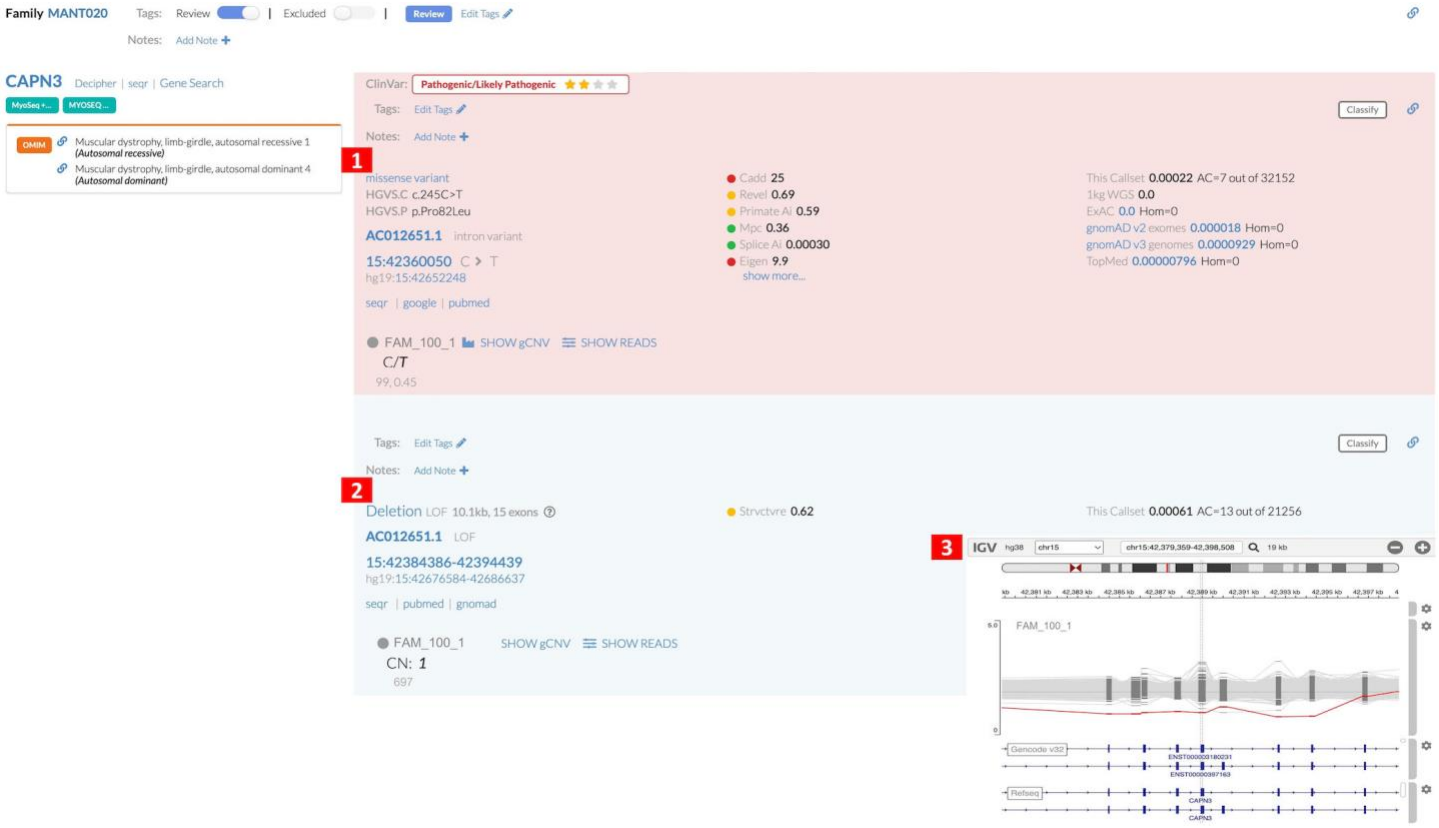
Paternal Ancestry: French

Imputed Population:
European (non-Finnish)

Features: Unaffected

- WES LOADED 5/26/2021
- WES - SV LOADED 5/25/2021
- WES LOADED 12/15/2020

Supplementary Figure S1: The *seqr* Family Page displaying FAM_100 as an example**.** (1) Family pedigree; (2) general description of the case; (3) analysis and case details entered by the analysis team; (4-6) individual level details including age, ancestry, sample QC information, clinical information using HPO terms; (7) variant search link to begin analysis and an overview of tagged variants on the hover over of the saved variants box, if the case was previously analyzed; (8) type and date of data loaded into *seqr*.



Supplementary Figure S2: Variant filtration of SNVs/indels and SVs in tandem. In this example, a recessive restrictive search identified (1) a missense variant and (2) deletion in *CAPN3.* Variants in the raw read data can be viewed using (3) IGV within *seqr*. Both variants were externally validated and reported as the diagnosis for this research participant with limb-girdle muscular dystrophy.

GNAI1

1

OMIM PubMed GeneCards Protein Atlas NCBI Gene GTEx Portal Monarch Decipher UniProt gnomAD MGI IMPC ClinVar HGMD

2 Basics

Symbol	GNAI1
Ensembl ID	ENSG00000127955
Description	Guanine nucleotide-binding proteins (G proteins) function as transducers downstream of G protein-coupled receptors (GPCRs) in numerous signaling cascades. The alpha chain contains the guanine nucleotide binding site and alternates between an active, GTP-bound state and an inactive, GDP-bound state. Signaling by an activated GPCR promotes GDP release and GTP binding. The alpha subunit has a low GTPase activity that converts bound GTP to GDP, thereby terminating the signal. Both GDP release and GTP hydrolysis are modulated by numerous regulatory proteins (PubMed: 8774883, PubMed: 18434541). Signaling is mediated via effector proteins, such as adenylate cyclase. Inhibits adenylate cyclase activity, leading to decreased intracellular cAMP levels (By similarity). The inactive GDP-bound form prevents the association of RGS14 with centrosomes and is required for the translocation of RGS14 from the cytoplasm to the plasma membrane. Required for normal cytokinesis during mitosis (PubMed: 17635935). Required for cortical dynein-dynactin complex recruitment during metaphase (PubMed: 22327364). {ECO: 0000250|UniProtKB:P10824, ECO: 0000269|PubMed: 17635935, ECO: 0000269|PubMed: 18434541, ECO: 0000269|PubMed: 22327364, ECO: 0000269|PubMed: 8774883}.
Coordinates	chr7:79768028-80226181 (hg19: chr7:79397344-79855497)
Gene Type	protein_coding

3 Stats

Coding Size	1.1kb
Missense Constraint	z-score: 2.628 (ranked 1563 most constrained out of 19704 genes under study) *NOTE: Missense contraint is a measure of the degree to which the number of missense variants found in this gene in ExAC v0.3 is higher or lower than expected according to the statistical model described in [K. Samocha 2014]. In general this metric is most useful for genes that act via a dominant mechanism, and where a large proportion of the protein is heavily functionally constrained. For more details see this README.*
LoF Constraint	louef: 0.3790 (ranked 3327 most intolerant of LoF mutations out of 19704 genes under study) pLI-score: 0.9113 (ranked 2989 most intolerant of LoF mutations out of 19704 genes under study) *NOTE: These metrics are based on the amount of expected variation observed in the gnomAD data and is a measure of how likely the gene is to be intolerant of loss-of-function mutations.*
Haploinsufficient	pHI-score: 0.9535 *NOTE: These are a score under development by the Talkowski lab that predict whether a gene is haploinsufficient based on large chromosomal microarray data set analysis. Scores >0.84 are considered to have high likelihood to be haploinsufficient.*
Triplosensitive	pTS-score: 0.7469 *NOTE: These are a score under development by the Talkowski lab that predict whether a gene is triplosensitive based on large chromosomal microarray dataset analysis. Scores >0.993 are considered to have high likelihood to be triplosensitive.*

4 Disease Associations

OMIM	*No disease associations*

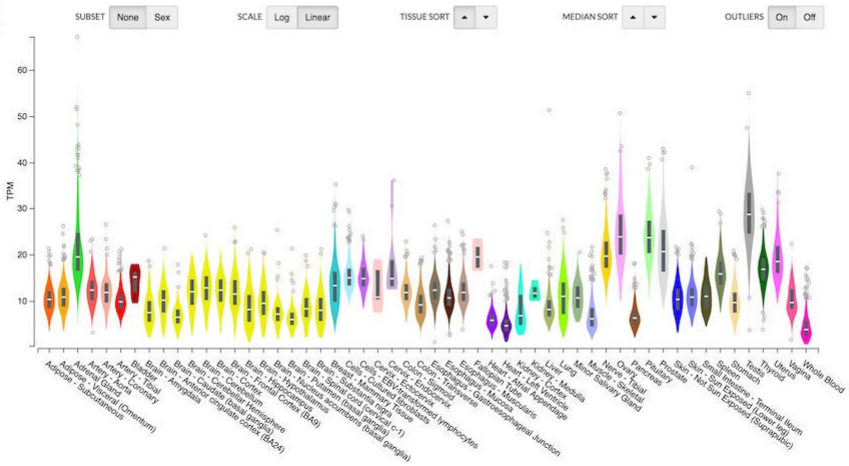
5 Shared Notes

Information saved here will be shared across seqr. Please consider using this space to share gene-specific information you learn while researching candidates.

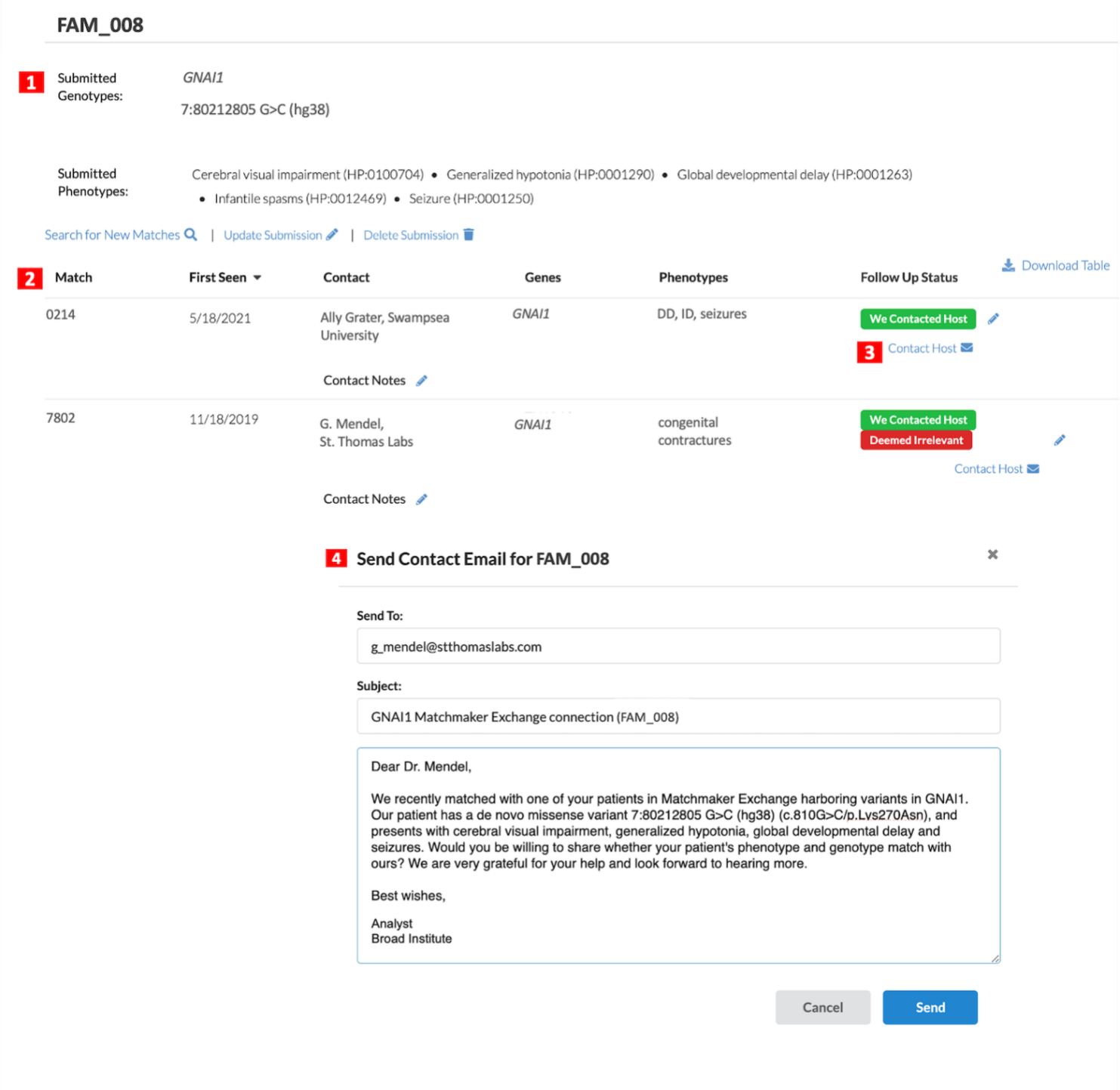
Variants in GNAI1 cause a syndrome associated with variable features including developmental delay, seizures, and hypotonia - PMC8107131 *By Broad Analyst (06/02/2021)*

Add Note +

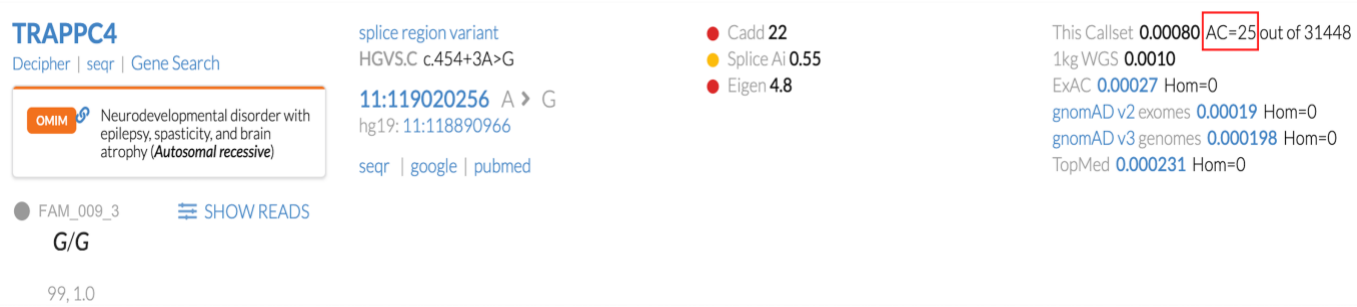
6



Supplementary Figure S3: Gene Page. Includes (1) links to external resources; (2) basic gene information; (3) gene constraint and dosage sensitivity details; (4) gene-disease relationships based on OMIM; (5) user notes shared across *seqr*; (6) GTEx tissue expression data.



Supplementary Figure S4: The Matchmaker Exchange node in *seqr*. (1) To make a submission, users select the variant and HPO terms listed in *seqr*; (2) MME matches are listed below with the host's contact details, gene ID, and phenotype, if included in the submission; (3) Automated email feature to communicate with hosts and track the status of matches within *seqr*; (4) sample contact email with variant and phenotype information.



Supplementary Figure S5: Allele count for a splice region variant in the gene *TRAPPC4* showing 25 alleles in the CMG callset. A review of the variants revealed three other cases with similar phenotypes that were homozygous for this variant across distinct projects and research groups.