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A Genome Sequencing Program for Novel Undiagnosed Diseases

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Abstract

Purpose—The Scripps Idiopathic Diseases of huMan (IDIOM) study aims to discover novel gene-disease relationships and provide molecular genetic diagnosis and treatment guidance for individuals with novel diseases using genome sequencing integrated with clinical assessment and multidisciplinary case review.

Methods—Here we describe the IDIOM study operational protocol and initial results.

Results—121 cases underwent first tier review by the principal investigators to determine if the primary inclusion criteria were satisfied, 59 (48.8%) underwent second tier review by our clinician-scientist review panel, and 17 (14.0%) patients and their family members were enrolled.

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60% of cases resulted in a plausible molecular diagnosis. 18% of cases resulted in a confirmed molecular diagnosis. 2 of 3 confirmed cases led to the identification of novel gene-disease relationships. In the third confirmed case, a previously described but unrecognized disease was revealed. In all three confirmed cases, a new clinical management strategy was initiated based on the genetic findings.

Conclusions—Genome sequencing provides tangible clinical benefit for individuals with idiopathic genetic disease, not only in the context of molecular genetic diagnosis of known rare conditions, but also in cases where prior clinical information regarding a new genetic disorder is lacking.

Keywords

clinical sequencing; rare disease; genomics; undiagnosed diseases; genome sequencing

INTRODUCTION

The traditional approach to rare, severely disabling medical conditions frequently leaves the affected individual without a diagnosis and effective treatment. Patients with such conditions can remain ill and endure a “diagnostic odyssey” for years, which is not only difficult for such individuals and their family, but can also be very cost inefficient. Many have previously suggested the utility of genomic information for diagnosing and treating such conditions, and early evidence of the successful application of whole exome sequencing (WES) and whole genome sequencing (WGS) for such purposes is emerging¹⁻⁶. Of the rare likely genetic diseases that have already been described, approximately half have yet to be linked to a causal gene (termed here: “idiopathic diseases”)⁷. Estimates of the total number of rare likely genetic diseases based on the number of known disease causing and essential genes have resulted in predictions of between 7,000 to 15,000 disorders, suggesting many rare genetic diseases have yet to be described⁸. While the application of genome sequencing to the molecular genetic diagnosis of previously described rare Mendelian disorders is essentially proven, the utility of genome sequencing in novel diseases has not been systematically explored. For example, of the ~100 patients successfully diagnosed by the National Institutes of Health Intramural Undiagnosed Disease Program (NIH UDP) (20–25% of the total enrolled), 15 cases (~3.5% of total enrolled) correspond to novel gene associations for previously described diseases, and only 2 cases (<1% of total enrolled) correspond to previously unknown diseases⁹.

The Scripps Idiopathic Diseases of huMan (IDIOM) study was initiated in 2011. IDIOM was, in large part, modeled after the NIH UDP, with a few exceptions. The primary exception being that we focus exclusively on cases that do not fit a previously described phenotype, or cases where the disorder matches a previously described phenotype and all known genetic causes of the disorder have been ruled out. In other words, only 17 of 100 successfully diagnosed cases in the NIH UDP would have qualified for the IDIOM study (15 corresponding to a novel gene associations for previously described diseases, 2 cases corresponding to previously unknown diseases). The application of genome sequencing to molecular genetic diagnosis in this sub-population of individuals presents some unique challenges both in terms of the evaluation of cases and appropriateness for the IDIOM

program, as well as for the ultimate return of genetic results. In this report we provide a description of IDIOM study procedures, the initial results from the first three years of operation, and the clinical benefit achieved by those realizing a confirmed genetic diagnosis.

METHODS

Recruitment and Screening

The Scripps Idiopathic Diseases of huMan (IDIOM) Study (IRB-11-5723) was approved by the Scripps Institutional Review Board in 2011. A separate informed consent was attained for genome sequencing vs. treatment response monitoring. Recruitment for IDIOM was done through announcements to physicians within the Scripps Health system and advocacy groups, announcements via local media^{10,11}, and word of mouth. A number of online sources were utilized such as the CTSA Vanderbilt-hosted Researchmatch.org, “reach out” to leaders of the NIH UDP, RARE Project, and National Organization for Rare Diseases. Scripps Health hosts a landing page for the IDIOM study that includes study criteria and coordinator contact information. The trial is also listed on clinicaltrials.gov (<http://clinicaltrials.gov/ct2/show/NCT01440218>). Since initial financial support for our study was limited, we have been conservative with respect to our recruitment efforts so as not to be inundated with a large number of referrals that we would not have the resources to fund.

Inclusion criteria for the study are the following: (1) the patient has a grave or serious condition that is undiagnosed despite extensive medical and genetic evaluation – for patients with a likely clinical diagnosis, at minimum, a gene panel test is required to rule out known genetic causes of the disorder; (2) the patient’s condition is potentially “actionable” or amenable to treatment – this is a subjective judgment by the physician review panel that typically only excludes individuals with severe dysmorphologies; (3) the condition appears genetic in origin; (4) the patient’s anticipated life expectancy is consistent with the study timeline for sequencing; and (5) the patient has a physician champion who is willing to work with the research team and take responsibility for returning genetic results to the patient.

In order to be considered, patients or their referring physician provide a short clinical summary and all available medical records. Referrals undergo an initial review by the IDIOM study coordinator. Typically, cases with complete medical records undergo another round of internal review by core study investigators, often via email, and those that appear to meet inclusion criteria are forwarded for review by the IDIOM Clinician-Scientist Review Panel.

Clinician-Scientist Review Panel

Our clinician-scientist review panel is made up of approximately 12 practicing physicians, as well as a research team consisting of bioinformatics and genetic analysis specialists, physicians who utilize genetics extensively in clinical practice, sequencing experts, ethicists, clinical psychologists, and research nurses. The Director of the Scripps IRB is also a member of the panel. The clinical disciplines represented among the physician members include, though are not limited to, the following: neurology, rheumatology, internal medicine, allergy/immunology, cardiology, medical oncology/hematology, and

gastroenterology/hepatology. For a quorum we required the presence of at least 5 physicians and 2 bioinformatics or sequencing experts. Selection of cases is made based on majority vote, however, in almost all instances to date, decisions to enroll a patient have been unanimous. The meetings typically last 1.5 hours, and between 3 and 4 cases are usually reviewed per session. We encourage and allow for, but do not require, the physician champion of patients whose cases are being reviewed to be available during the meeting (either in person or via teleconference) in order to answer questions and interface with the panel.

Consent and Enrollment

Once a case has been selected by the clinician-scientist panel, our nurse study coordinator consents the patient and family members. Usually the participants that comprise a case are those in a trio (i.e., proband, mother, and father), but occasionally other biological family members are sequenced, and in these instances, it is usually a sibling of the proband or parents.

Importantly, a primary issue raised in the literature regarding patient consent for WES and WGS studies is the identification of ‘incidental’ or ‘secondary’ findings (i.e., genomic findings of clinical relevance that are not recognized as being associated with the presenting disease/condition). We have deemed that best practices are yet to be determined by empirical data¹² and thus, have elected to only return results directly relevant to the presenting indication. If we should inadvertently discover incidental findings that could have an effect on the patient’s health, the results would be reviewed by our clinician-scientist review panel, who would adjudicate how to proceed with informing the physician champion and patient¹³.

For selected cases, we also ask the patient’s physician champion (usually the referring physician) to sign an agreement of participation that stipulates that s/he will commit to: (a) regular interactions with the research team; (b) acceptance of responsibility for return of genomic results to the patient; (c) acceptance of any clinical decision-making on the basis of any results provided; and (d) completion of brief baseline and follow-up questionnaires and/or interviews pertaining to the study.

Sequence Data Generation, Analysis and Interpretation

Once cases have been selected and patients and family members are consented for participation, blood is drawn and brought to our lab at STSI for sequencing of the proband and biological family members. Once parentage is confirmed, WES is performed for the detection of coding variants, and low pass WGS is performed for the detection of structural and copy number variants. Target WES coverage is ~100× and target low pass WGS coverage is ~5×. Other published papers have described this data generation protocol in detail, as well as our methods for analysis and interpretation^{14–17}. If necessary, especially for indels or variants with limited coverage in any family members, Sanger sequencing is utilized to confirm candidate causal variants. The theoretical target breakpoint resolution for low pass WGS detection of CNVs is 200bp given a bin size of 200–300bp and target coverage of 4–8×¹⁸. This resolution allows for the identification of small events such as single exon deletions. In practice, this resolution was achieved; however manual inspection

of read level data of the WES and low pass WGS data was required due to false positive variant calls. Ultimately, algorithms such as Genome STRiP, which utilize population level data to account for systematic read depth biases, are necessary to improve the reliability of these results¹⁹.

Sequencing is performed in a research laboratory with results ultimately returned to the physician champion. Given the exploratory nature of these cases, results as well as the consent process include an explanation that any findings are unproven in nature and performed in an uncertified laboratory. Our case selection process, i.e. the focus on novel phenotypes and novel gene-disease relationships, eliminates from consideration individuals likely to benefit from certified laboratory tests, and we provide suggestions for the appropriate alternative commercial certified laboratories for these patients. Similarly, if a known pathogenic variant is identified, recommendations for CLIA confirmation via validated tests (rather than CLIA confirmation in a certified lab without the specific validated test) are provided.

Individualized Genomic Report and Return of Results

Once results for a specific patient have been generated, an individualized genomic report is prepared for dissemination to our Clinician-Scientist Review Panel and the patient's physician champion. The panel has the opportunity to raise any issues related to the specific case prior to disclosing results. In all cases, one or more consultations between members of the panel and the physician champion are arranged to allow him/her to have any questions answered and have the results verbally conveyed. In cases where a plausible diagnosis is identified, the discussion with the physician champion centers on whether or not the findings should change clinical management of the patient. Any new treatment offered to the patient is ultimately the treating physician's decision. Certified genetic counselors are available on demand if requested.

Follow-up Studies

While STSI houses the facilities required for functional studies, specialized assays are often required for appropriate functional characterization of candidate disease causative variants. Thus, to functionally characterize findings in IDIOM, appropriate follow-up studies are tailored to the disease and gene in question, and we generally do this in collaboration with other laboratories specialized in the study of a particular gene or gene family. STSI is also uniquely facile in the use of wireless sensors. Thus, when appropriate for select patients, we design and deploy N-of-1 studies for quantitative assessment of physiologic metrics. Furthermore, we have used such approaches to objectively determine whether there has been a therapeutic response to treatment once a molecular diagnosis is made and a genomically-indicated treatment initiated.

RESULTS

Referrals and Enrolled Patients

In the first three years of the IDIOM program, 121 patient referrals were received, 59 (48.8%) have undergone second tier review by our clinician-scientist review panel, and 17

(14.0%) patients and their family members have been enrolled. Referrals have come from over 16 different U.S. states, and we have received a number of international referrals.

Demographic statistics and comparisons for referred versus reviewed versus enrolled patients are shown in Table 1. Across all of the 121 patients referred to date, 31.9% were children (i.e., <18 years of age), 59.4% female, and 36.7% physician referred (versus self or family referred). As shown, however, those cases that underwent panel review and/or that were eventually enrolled were younger and more likely to be physician referred. Self/family referred subjects, if selected, were required to secure a physician champion.

Figure 2 shows the medical specialties/phenotypes represented among the 121 patients referred to date for which clinical information was available. By far the most common category has been neurologic disorders, encompassing 32.1% of referrals, with hematology/oncology, allergy/immunology, cardiology, and gastroenterology making up the top five broad phenotypic categories.

The major reasons for exclusion of cases have been identification of cases that meet a previously described phenotype and exclusion of cases that do not appear to be genetic. Cases that meet a previously described phenotype, e.g. when the submitted case already has a likely clinical diagnosis, are referred to an appropriate laboratory, or appropriate test, upon exclusion. If all known genetic causes of the previously described phenotype are ruled out, the case would be reconsidered. Exclusion of cases not likely to be genetic is usually based on one of the following reasons; 1) the panel feels the condition is likely explained by an environmental insult or infectious disease, 2) unusual circumstances surrounding birth, for example pre-term birth or complications during birth – suggesting non-genetic developmental defect, 3) lack of objectively documented findings either on physical examination or testing, especially subjective symptoms that cannot be connected via dysfunction of a specific biological system.

Molecular Diagnosis

Detailed descriptions of each case and the findings are provided in the Supplemental Text. Of the cases that have been processed to date, we have arrived at a plausible molecular diagnosis in approximately 60% and a confirmed molecular diagnosis in approximately 18% of all cases (Table 2). A plausible molecular genetic diagnosis is defined as meeting the following criteria: 1) identified variants segregate in the family and reference populations in a manner consistent with the segregation of the disease in the family and incidence of the disorder in the general population, 2) variants influence the coding/splicing of a protein coding gene, and 3) the gene can be connected to the presenting phenotype through similar human disorders caused by mutation in the same gene or via genome-wide association studies, the gene can be connected to the presenting phenotype through close functional interaction with genes known to cause the presenting phenotype or similar phenotype, or the gene can be connected to the presenting phenotype via animal studies. Of the 60% of cases meeting this criteria, we have aggressively pursued functional validation in cases where the variant is of de-novo origin, further increasing confidence in the finding and maximizing yield of downstream effort with collaborators. In 2 cases so far we have completed functional and statistical confirmation of a novel gene-disease relationship via the

identification of additional affected subjects with mutations in the same gene as well as functional confirmation of gene dysfunction^{15,17}, and in one instance a previously identified pathogenic variant was revealed. In all three cases, a new management strategy (pharmacological treatment) was initiated based on the findings, and we are currently closely monitoring this patient's response to the therapy.

Clinical Management Strategy Changes and Benefit

IDIOM1 presented with a complex movement disorder, described in detail in Chen et al. 2014¹⁵, ultimately confirmed to be due to a gain of function de-novo mutation in *ADCY5*, and potentially modified by additional mutations in *DOCK3* (unconfirmed). An N-of-1 style trial to monitor night time abnormal movements during treatment with various compounds indicated by gain of function in *ADCY5* (ropinirole, carbamazepine, tetrabenazine, diazepam) with appropriate run-in and washout periods was initiated. The trial was halted upon request subsequent to initiation of the first agent, diazepam, after complete resolution of night-time myoclonic jerks. Diazepam has been previously shown to abrogate stress tolerance in *ADCY5* null mice²⁰. Figure 3 presents a dramatic and sustained resolution of abnormal movements after initiation of diazepam treatment, as captured by a movement-tracking device.

IDIOM9 presented with a complex seizure disorder with drop attacks, described in detail in Torkamani et al. 2014¹⁷, ultimately confirmed to be due to a de-novo mutation in potassium channel *KCNB1* which changed ion selectivity. As a result, in order to control potassium levels carefully, the subject was placed on a specialized diet and kept hydrated. Thus, a change in the clinical management strategy was initiated, with unconfirmed clinical benefit. Unfortunately, no particular anti-epileptic drug is indicated from the genetic results, and comparison to patients with a similar underlying genetic cause of epilepsy did not reveal a specific and efficacious therapeutic strategy²¹ (personal communication). An anecdotal reduction in drop attacks has been noted by the treating physician, though longer follow-up is required to confirm a sustained benefit.

IDIOM15 presented with hypertrichotic osteochondrodysplasia (excess hair growth on scalp, forehead, and face), a gene defect that was ultimately attributed to a known pathogenic de-novo *ABCC9* mutation. Dominant missense mutations in *ABCC9* cause gain-of-function channel opening and implicate a number of different channel blockers as potential therapeutic avenues²². Treatment modifications have been initiated with long-term follow-up required to confirm a sustained benefit.

DISCUSSION

The Scripps Idiopathic Diseases of huMan (IDIOM) study aims to discover novel gene-disease relationships and provide molecular genetic diagnosis and treatment options for individuals with idiopathic diseases using genome sequencing integrated with clinical assessment and multidisciplinary case review. The primary difference relative to other similar programs is our exclusive focus on novel gene-disease relationships. In fact, candidates with phenotypes similar to those previously described must have had known genes potentially mediating their phenotype ruled out before consideration as an IDIOM

subject. While our protocol exclusively focuses on novel diseases or novel gene-disease relationships, it is remarkable that we demonstrate an initial rate of novel and confirmed genetic discoveries similar to that reported by programs focused on standard molecular genetic diagnosis via genome sequencing (20–25%)^{4,9,23,24}. Although the volume, rate, and efficiency at which novel gene-disease relationships can be confirmed is lower than that achievable by standard molecular genetic diagnosis via genome sequencing, these results suggest that genome sequencing has the potential to be at least as efficacious in providing genetic diagnosis for individuals with previously undescribed disease as it is for individuals with known Mendelian disorders – with an upper limit to the diagnostic yield of ~60% ($\pm 23\%$ – 95% confidence interval) as informed by our plausible findings. However, we must acknowledge that a direct comparison between the diagnostic rate of these programs cannot be made since the rate depends heavily upon the ascertainment of the cohort in question.

The conversion of novel, plausible, gene-disease relationships to confirmed and validated genetic diagnoses should increase the yield of clinical genome sequencing programs above the current 20–25% diagnostic rate. In fact, individuals sequenced at clinical genome sequencing centers have initiated contact with the Scripps IDIOM investigators, subsequent to publication of our confirmed novel gene-disease relationships, bringing to light the fact that some individuals do not achieve a genetic diagnosis due to a lack of recognition of the causal variant in genome sequence data by those reporting the results, rather than any deficit in the technical identification of the causal variant. For example, we have received inquiries from two individuals with negative clinical exome results who had the same de-novo *ADCY5* mutation as described in our IDIOM1 case – reported, correctly at the time of the test, as a variant of unknown significance in the clinical exome report. It remains to be seen what the relative contribution of deficits in technical variant identification vs. deficits in knowledge of gene-disease relationships is to the lack of molecular genetic diagnosis in those ~75% of individuals not receiving a genetic diagnosis after clinical genome sequencing. Ultimately, the contribution of novel gene-disease relationships to increasing the yield of clinical genome sequencing requires conversion of plausible findings to a confirmed genetic diagnosis through the identification of additional cases. This has been difficult to achieve but may be facilitated through services such as Matchmaker Exchange (matchmakerexchange.org). Comprehensive and accessible collection of phenotypic characteristics is key to achieving this goal.

In our study, all confirmed molecular genetic diagnoses achieved a tangible clinical benefit above and beyond the utility achieved simply by ending a diagnostic odyssey. However, there have been some notable challenges in the context of this project. For example, we often have families request other information, frequently referred to as secondary or “incidental findings” from their genomic analysis, and the research team has engaged in substantial discussion as to whether findings that do not pertain to the patient’s presenting condition should be assessed and reported back to the physician and/or patient. At this time, given that sequencing is performed in an uncertified laboratory for a pre-specified purpose, we do not return information that is not directly applicable to the presenting condition. We have also observed wide variability in the extent to which our “physician champions” have knowledge of and comfort with genomic information, which has a major influence on the amount of information these clinicians then share with patients and the ultimate clinical

utility of any findings. A multi-disciplinary clinician-scientist review panel has been essential to supporting physician champions as well as selection of appropriate cases most likely to benefit from genome sequencing. Finally, the transmission of information back to physician champions, clearly indicating the suggestive nature of the majority of our findings, has been essential to managing expectations of the physician champions and ultimately the enrolled subjects.

An important area of improvement, especially for this program with no specific disease focus, is to objectively link the symptoms presented by study subjects to previously described conditions. Any physician-scientist review panel is unlikely to represent specialties covering the broad range of conditions referred to the program, thus similarities to previously described conditions (as exemplified by our hypertrichotic osteochondrodysplasia case) can be missed. In a more comprehensive program, spanning molecular genetic diagnosis of undiagnosed disease and discovery of novel gene-disease relationships in idiopathic disease, automated systems for phenotype matching can provide both known genetic conditions and gene-disease relationships that should be considered for confirmatory molecular diagnosis, as well as grounding for exploration of novel gene-disease relationships through implicated biological processes and genetic networks mediating those processes. We believe this could provide a model for the unbiased application of genome sequencing across all rare genetic disorders, known and unknown.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Conflict of Interest

Ashley Scott-Van Zeeland, Eric Topol, Ali Torkamani, and Nicholas Schork declare they are co-founders and equity holders of Cypher Genomics, Inc.

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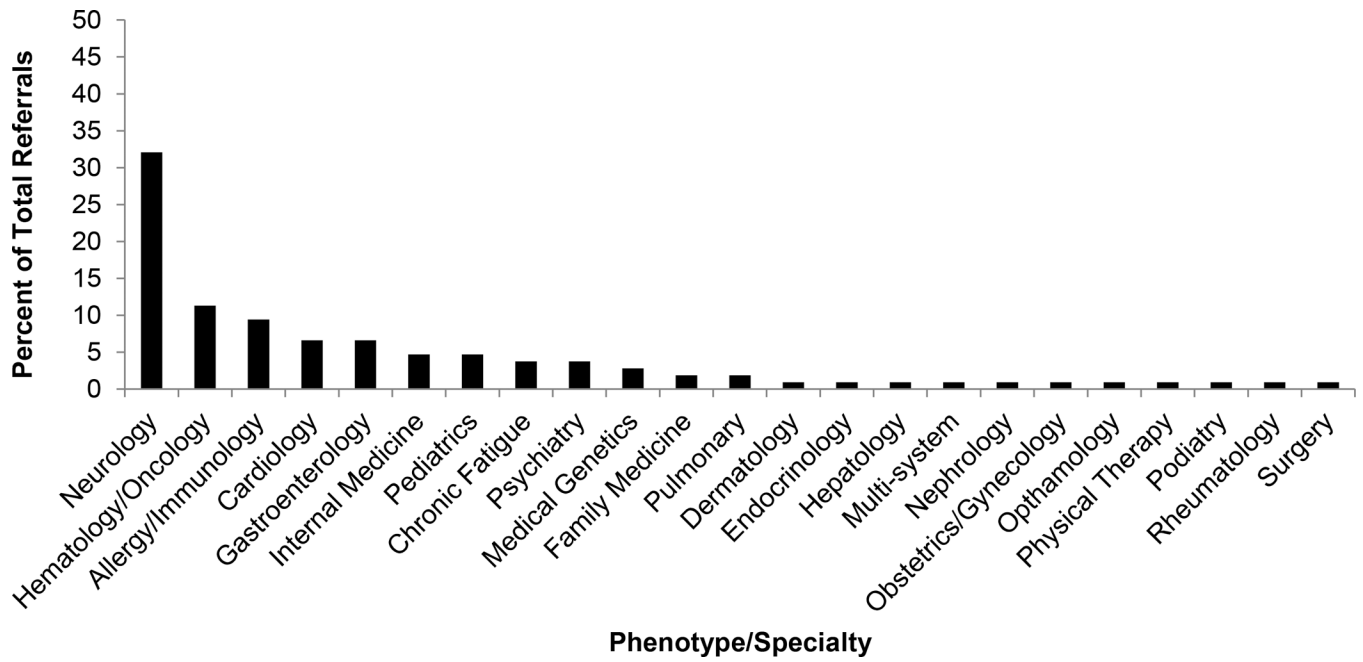


Figure 1. Phenotypic Distribution of Case Referrals

The distribution of phenotypes referred to the Scripps IDIOM study is plotted based on the subset of N = 106 referrals for whom we were able to obtain complete data.

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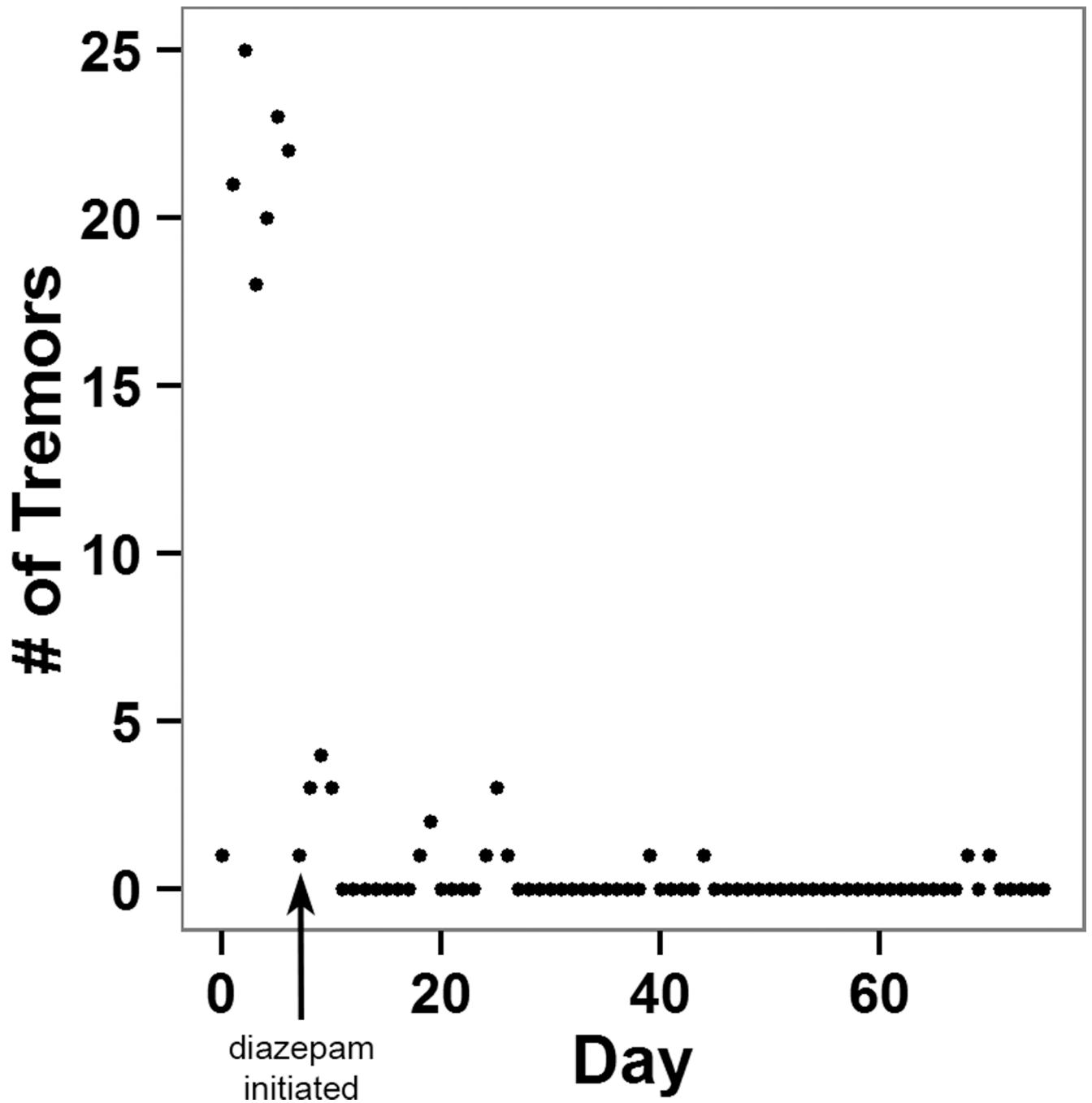


Figure 2. Tracking of Therapy Response in IDIOM1

Actigraphy based motion tracking demonstrates a dramatic and sustained decrease in night time myoclonic jerks due to gain of function mutation in *ADCY5*. Day 0 – 6 represents the last week of a three week run-in period to wash-out previous therapies. Diazepam is initiated on day 6 (arrow) with a dramatic reduction tremors sustained for over two months. Tremors are defined as movement magnitude >0 sustained for greater than 60 seconds.

Table 1
Demographic Characteristics of Referred, Reviewed and Enrolled Cases

Demographic characteristics of referred, reviewed, and enrolled subjects.

Variable	Referred (not Reviewed/ Enrolled)	Panel Reviewed (not Enrolled)	Enrolled	Referred vs. Reviewed	Reviewed vs. Enrolled
N	62	42	17	NA	NA
Age Years (Mean, SD, Range)	42.8 (22.7) <1 – 77 ¹	26.0 (18.5) <1 – 67 ³	18.8 (16.0) <1 – 44.0	.001	.165
Gender (Female)	63.8% ²	47.6%	76.5%	.124	.043
Children (<18 Years)	15.6% ¹	35.7%	52.9%	.054	.222
Referral from Physician	30.6%	31.7% ⁴	70.6%	.909	.006

¹Based on the subset of N = 32 referrals for whom we were able to obtain data;

²Based on the subset of N = 47 referrals for whom we were able to obtain data;

³Based on the subset of N = 39 referrals for whom we were able to obtain data;

⁴Based on the subset of N = 41 referrals for whom we were able to obtain data

Table 2

Genetic Diagnoses of Enrolled Cases

Case	Phenotype	Outcome	Plausible Diagnosis	Functional Confirmation
1	Complex Movement Disorder	<i>ADCY5</i> de-novo gain of function mutation	yes	Yes
2	Lymphoproliferative Disorder	Plausible inherited candidate causative mutations in <i>GIMAP8</i>	yes	not performed
3	Inflammatory Bowel Disease	Plausible inherited candidate causative mutations in <i>MST1R</i>	yes	not performed
4	Fibromyxoid sarcoma	No cause identified	no	N/A
5	Immunodeficiency	No cause identified	no	N/A
6	Lipomatosis and Vasculitis	Plausible inherited candidate causative mutations in <i>NR1P1</i>	yes	not performed
7	Skin and Neurological Disorder	Potential, unconfirmed, diagnosis of subtype of Epidermolysis Bullosa due to inherited mutations in <i>DST1</i>	yes	Ongoing
8	Developmental Delay	No cause identified	no	N/A
9	Epileptic Encephalopathy	<i>KCNB1</i> de-novo missense mutation and confirmed KV2.1 dysfunction	yes	Yes
10	Developmental Delay	Plausible inherited candidate causative mutations in <i>SYNPO</i>	yes	ND
11	Familial Coronary Artery Disease	Plausible inherited candidate causative mutation in <i>TDG</i>	yes	Ongoing
12	Muscular Atrophy	No cause identified	no	N/A
13	Infantile Seizures	No cause identified	no	N/A
14	Recurrent Fever	Potential, unconfirmed, diagnosis of subtype of Chédiak–Higashi syndrome due to inherited mutation in <i>LYST</i>	yes	N/A
15	Congenital Hypertrichosis	Known pathogenic de-novo <i>ABCC9</i> mutation identified	yes	yes
16	Suspected autosomal dominant Opitz G/BBB	ongoing	N/A	N/A
17	Plastic Bronchitis	ongoing	N/A	N/A