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Pushing the boundaries of rare disease diagnostics with the help of the first Undiagnosed Hackathon

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In the first-ever Undiagnosed Hackathon, nearly 100 experts from 28 countries combined advanced phenotyping and genomic techniques for 48 hours, ultimately providing diagnoses to 40% of the previously undiagnosed families. This inspiring model demonstrates the power of multidisciplinary collaboration and patient partnership in precision diagnostics.

Hundreds of millions of people live with rare, undiagnosed conditions worldwide, comprising a significant public health challenge. There are between 7,000 and 11,000 known rare diseases collectively affecting 3.5–5.9% of the global population, with 72–80% believed to have a genetic basis[1]. Despite significant advances in genomic medicine, around 60% of patients with rare diseases remain undiagnosed even after comprehensive genomic testing[2,3]. Their diagnostic odysseys can span decades, leading to considerable emotional, financial and social burdens. Patients often face stigma, isolation, uncertainty and delays in accessing therapies[4]. This situation is worsened by a lack of awareness and limited access to advanced diagnostic genomic technologies, especially in low- and middle-income countries (LMICs)[5].

A timely and precise diagnosis can significantly improve patient care by providing a better understanding of potential symptoms or complications, which may help avoid unnecessary invasive diagnostic procedures and potentially dangerous treatments. A diagnosis guides early decisions about follow-up and management, such as targeted therapies, risk (for example, cancer) surveillance, genetic counseling and prenatal diagnostics. The rapid advancement of precision therapies for previously untreatable rare diseases underscores the importance of an accurate diagnosis[6]. Moreover, a diagnosis provides individuals with credibility for their illness, enables them to connect with patient organizations, and can bring relief to patients and caregivers by providing knowledge about how the condition will affect their lives.

Critical steps to shorten patients' diagnostic odysseys include (i) developing new diagnostic technologies and analysis tools, (ii) accelerating the rapid integration of these technologies into clinical practice, (iii) promoting global collaboration and (iv) facilitating secure data sharing[7]. A comprehensive catalog of rare diseases is also

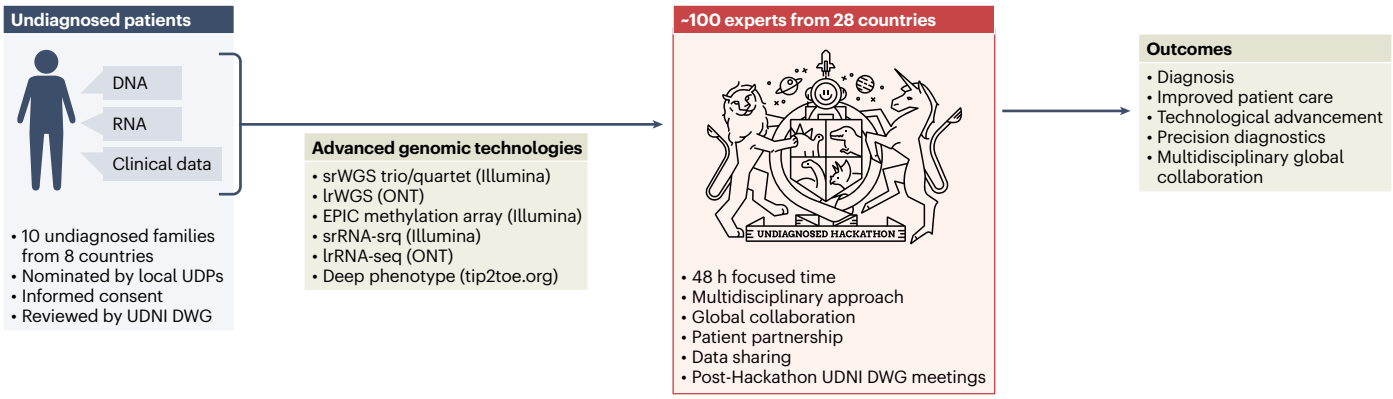

Fig. 1 | Logistical setup of the Undiagnosed Hackathon. Ten undiagnosed families from eight UDPs were selected to participate, and informed consent was obtained. Blood samples from the probands, parents and affected siblings were processed two months before the event. Proband and family DNA samples were analyzed using trio/quartet srWGS. Proband DNA and RNA samples underwent srRNA-seq, lrWGS, lrRNA-seq and EPIC methylation array genotyping. Deep phenotype data was collected by the local UDPs using https://tip2toe.org. During the 48-hour event, nearly 100 experts from 28 countries came together to analyze the comprehensive phenotype and genomic data in multidisciplinary teams, named the Smileys, Dinosaurs, Animals, Unicorns and Space. The six Swedish patients, including two pairs of affected siblings, and their families were present at the event for in-person evaluation. Four of the 10 families received a definite diagnosis (40%). The Undiagnosed Hackathon model serves as a model for knowledge transfer, diagnostic development, fostering of global multidisciplinary collaboration and patient partnership, benefiting the rare-disease community. The logo of the First Undiagnosed Hackathon was designed by Y. Asano for the Wilhelm Foundation, which holds all legal rights.

necessary, and it should include phenotype and genotype data[8] and be supported by mandatory international cooperation frameworks[9].

The ultimate aim of the Undiagnosed Diseases Network International (UDNI) is to provide answers for patients and families affected by undiagnosed conditions by fostering knowledge and technology exchange and enhancing global diagnostic capabilities, especially in resource-limited settings[10]. The Wilhelm Foundation (https://wilhelmfoundation.org/), a global organization for people living with an undiagnosed disease, co-founded the UDNI together with the NIH Undiagnosed Diseases Program[11,12].

The idea behind the first Undiagnosed Hackathon

A hackathon is an event in which participants engage in intensive, collaborative problem-solving over a short period. Originally created as a tech innovation strategy, hackathons have expanded into other fields, including medicine and healthcare (https://sv.ai/undiagnosed-1, https://hacking-health.org/), as a means of promoting interdisciplinary collaboration to solve complex challenges.

In June 2023, the Wilhelm Foundation, the Karolinska Undiagnosed Diseases Program (UDP) and PhenoTips held the first Undiagnosed Hackathon on site at Karolinska University Hospital and Karolinska Institutet (KI) in Stockholm, Sweden, with the vision of advancing rare disease diagnosis and encouraging global collaboration while raising awareness for undiagnosed diseases.

During the 48-hour event, nearly 100 experts from 28 countries came together to work on comprehensive genomic and phenotypic data from 10 undiagnosed families. A broad range of computational tools and a multidisciplinary approach were utilized, including the unique possibility of meeting the four participating Swedish undiagnosed families in person (https://www.undiagnosedhackathon.org/).

Before the event

Patient and participant selection. The UDNI Diagnostic Working Group (UDNI DWG) invited all UDNI members to nominate undiagnosed patients from their local UDPs based on the following inclusion criteria: (i) a strong suspicion of a monogenic disease, (ii) the patient remaining undiagnosed despite thorough diagnostic assessments, including prior genetic testing with at least exome sequencing singleton analysis, and (iii) written informed consents from patients or their legal guardians. Thereafter, the organizers selected 13 undiagnosed patients from 10 families (3 with 2 affected siblings) from China, Ghana, the Democratic Republic of the Congo, India, Pakistan, Sweden, Turkey and the USA. One patient with syndromic features was included even though genetic testing was entirely unavailable. All patients were discussed in the UDNI DWG forum and virtual meetings prior to the hackathon.

The organizers used an invitation-only model to bring around 100 global experts in rare disease diagnostics to Stockholm, including clinicians, geneticists, bioinformaticians, molecular biologists, scientists, developers, industry representatives, patient organizations and the 4 undiagnosed Swedish families, 2 of which had pairs of affected siblings (Fig. 1).

Technologies. Blood samples were provided two months in advance and processed by the Clinical Genetics and Genomics Department at Karolinska University Hospital in Stockholm. DNA and RNA were sequenced at the SciLifeLab Clinical Genomics and National Genomics Infrastructure units in Stockholm and Uppsala. Parents and affected probands were analyzed using trio or quartet short-read whole-genome sequencing (srWGS) (Illumina). Proband samples underwent short-read RNA sequencing (srRNA-seq) (Illumina), long-read whole-genome sequencing (lrWGS), long-read RNA sequencing (lrRNA-seq) (Oxford Nanopore Technologies) and methylation EPIC arrays genotyping (Illumina) (Fig. 1). Short-read trio whole-exome sequencing (srWES) (Illumina), trio lrWGS and singleton lrRNA-seq (Pacific Biosciences) data were available for the Chinese proband. Systematic and standardized phenotype data were collected at the local UDP using the open-source phenotyping tool tip2toe, developed by the Karolinska

UDP in collaboration with the Wilhelm Foundation and the UDNI DWG (https://tip2toe.org).

IT infrastructure. Hackathon participants were given access to the extensive phenotype and genotype data via KI's IaaS Virtual Server and an in-house open-source variant interpretation tool, SCOUT (https://github.com/Clinical-Genomics/scout). Broadband speed and IT security were optimized for the event.

During the event

Patient participation. The Undiagnosed Hackathon began with a welcome from the Wilhelm Foundation and the parents of the four undiagnosed families from Sweden, their six affected children and their unaffected siblings. The undiagnosed Swedish patients and their families were available for questions and clinical examinations.

Interdisciplinary and international team approach. The Undiagnosed Hackathon participation was exceptionally diverse and multidisciplinary, integrating the expertise of academia, healthcare, industry and patient organizations. This provided a unique opportunity for collaboration between these diverse disciplines, leading to the exploration of new approaches to tackle the diagnostic odyssey. This was further enhanced by the participation of experts from LMICs, who provided fruitful and essential insights.

The organizers divided participants into 5 teams, each comprising approximately 20 members from different countries with diverse expertise covering phenotyping, molecular and clinical genetics, and modern genetic technologies. Each team was assigned two or three undiagnosed patients and a designated room. The teams had complete freedom in how to tackle the challenge, including the choice of phenotype- or genotype-first approaches. The teams then spent 48 hours analyzing data, consulting with each other and directly engaging with the patients and their families. Participants were encouraged to express ideas, take risks, and explore innovative pathways.

Outcomes of the event. Four out of ten families (40%) received a definitive diagnosis on the first day. Successful approaches and tools were rapidly shared among teams through digital collaborative communication tools and summary meetings. Unsolved cases were redistributed for further analysis, but these cases were more challenging because no convincing disease-causing variants had been identified. Candidate genes were identified in four additional families, and recommendations for further examinations were generated for all undiagnosed families.

The phenotypes and disease-causing variants of the solved cases are shown in Table 1. All diagnoses had a direct impact on patient management and/or genetic counseling, including the possibility of prenatal testing. One patient was diagnosed with Costello syndrome (MIM 218040) caused by a de novo variant in *HRAS*, leading to cardiac and cancer surveillance. Another patient, previously diagnosed with cerebral palsy, was diagnosed with a neurodevelopmental disorder with autism and seizures (MIM 619239) caused by a de novo variant in *CUL3*. A third patient was diagnosed with hypotonia, infantile, with psychomotor retardation and characteristic facies 3 (MIM 616900) due to compound heterozygous variants in *TBCK*. lrWGS data enabled precise mapping of the deletion, while srRNA-seq confirmed the impact on gene expression and splicing (Table 1). This diagnosis immediately revealed the patient as suitable to start treatment with branched-chain amino acids (Bramino). Finally, the fourth patient was homozygous for a pathogenic variant in *IGHMBP2* causing spinal muscular atrophy with respiratory distress type 1 (MIM 604320), a possibility that had been dismissed through commercial genetic testing with whole-exome sequencing, emphasizing the importance of considering the technical limitations of available tests (Table 1).

After the event

All identified disease-causing variants were reassessed in a clinical setting at Karolinska University Hospital using standardized American College of Medical Genetics (ACMG) criteria[13] and submitted to ClinVar (Table 1). Findings were communicated to the relevant families by the referring physicians at their local UDPs.

Efforts to diagnose the remaining families continued nine months after the hackathon, including monthly online UDNI DWG meetings to discuss updates and next steps. Although no further patients were diagnosed, patients and parents found comfort in knowing that every possible effort was made to find a diagnosis.

Conclusions and recommendations for future Undiagnosed Hackathons

The Undiagnosed Hackathon demonstrates, in a practical setting, the potential of global collaboration, patient engagement, cutting-edge technology and a multidisciplinary approach in addressing the diagnostic gap in rare diseases[14]. It provides a platform for informal learning, problem-solving and collaboration, fostering a sense of community within the UDNI and the rare diseases field.

The participants' diverse backgrounds allowed a comprehensive approach to problem-solving and served as a remarkable platform for networking opportunities and knowledge transfer across disciplines and countries. The patients' presence and stories instilled a profound sense of meaning and reaffirmed the 'patient at the center' ethos. Fostering partnerships among diverse stakeholders enhanced the overall value and impact of the event. The combination of protected time to focus solely on a specific task and the collaborative spirit whereby participants gave each other appreciation, feedback and social support created a psychologically safe space[15] that clearly stimulated creativity and innovation and challenged participants to give their best, pushing the boundaries of genomic diagnostics beyond what is readily achievable in everyday healthcare.

One of the challenges faced was the need for integrated analysis solutions and expertise for handling complex multi-omics data, which limited the ability to fully utilize the data available. Future hackathons would benefit from providing the data to participants beforehand, which requires careful coordination between referring UDPs and courier services to ensure timely collection of samples and phenotype data. It is also critical to have in place an IT infrastructure with fast, secure data transfer protocols to facilitate data access. Offering training sessions before the event could help participants manage the complex datasets. Because of the limited timeframe, we recommend that future hackathons focus on well-phenotyped undiagnosed patients who have undergone trio srWGS prior to inclusion. Although clinical expertise is crucial for accurate diagnosis, increasing the number of bioinformaticians and researchers on functional studies could further improve the diagnostic yield. Despite the cost involved, the Undiagnosed Hackathon should keep the in-person format to provide a unique networking platform and hands-on opportunities to evaluate the clinical utility of new genomic technologies. Having industry experts on site to support the teams in using these technologies further strengthens the educational value of the event.

Table 1 | Clinical characteristics of the patients diagnosed during the first Undiagnosed Hackathon and the variants identified

Patient ID, age, gender and country of origin	HPO terms	Genetic investigations prior to the Undiagnosed Hackathon	ClinVar SCV	HGVS variant description	Variant classification	Classification criteria according to ACMG guidelines, 2015	Diagnosis (OMIM)
HACK0005 6-year-old male Sweden	HP:0011436 Abnormal maternal serum screening; HP:0034058 Abnormal fetal morphology; HP:0010880 Increased nuchal translucency; HP:0030917 Low APGAR score; HP:0002643 Neonatal respiratory distress; HP:0001999 Abnormal facial shape; HP:0000490 Deeply set eyes; HP:0000341 Bitemporal narrowing; HP:0011220 Prominent forehead; HP:0002058 Myopathic facies; HP:0000414 Bulbous nose; HP:0000463 Anteverted nares; HP:0010804 Tented upper lip vermilion; HP:0025252 Geographic tongue; HP:0006482 Abnormal dental morphology; HP:0000168 Abnormality of the gingiva; HP:0012443 Abnormality of brain morphology; HP:0001263 Global developmental delay; HP:0002187 Intellectual disability, profound; HP:0002465 Poor speech; HP:0001250 Seizure; HP:0001252 Hypotonia; HP:0000028 Cryptorchidism; HP:0001410 Decreased liver function; HP:0002019 Constipation; HP:0011968 Feeding difficulties	CMA and WES trio; single-gene testing for *DMPK, SMN1, SMN2, FMR1, SERPINA1*. (confirmed α-1 antitrypsin deficiency)	SCV005091969	NM_001163435.3(*TBCK*): c.2060-6793_2235+427del	Pathogenic	Deletion affects exon 23 of *TBCK*. RNA-seq shows exon skipping of exon 23, and loss-of-function variants in *TBCK* are known to be pathogenic (PMID: 27040692, 30103036). Disruption of exon 23 has been observed in individuals with TBCK-related conditions (Variation ID: 978028). This patient is compound heterozygous with another pathogenic variant in *TBCK* (NM_001163435) c.382-2A>G. (PVS1, PM2, PM3.)	Hypotonia, infantile, with psychomotor retardation and characteristic facies 3 (OMIM:616900) (AR)
			SCV005091970	NM_001163435.3(*TBCK*): c.382-2A>G	Pathogenic	Sequence change affects an acceptor splice site in intron 4 of *TBCK*. Sequencing of cDNA shows exon skipping of exon 5, and loss-of-function variants in *TBCK* are known to be pathogenic (PMID: 27040692, 30103036). Disruption of this splice site has been observed in individuals with TBCK-related conditions (Variation ID: 1488790). This patient is compound heterozygous with another pathogenic variant in *TBCK* (NM_001163435) c.2060-6793_2235+427del. (PVS1, PM2, PM3.)	
HACK0006 5-year-old female Sweden	HP:0001562 Oligohydramnios; HP:0034059 Abnormal fetal physiology; HP:0001511 Intrauterine growth retardation; HP:0001558 Decreased fetal movement; HP:0025116 Fetal distress; HP:0030917 Low APGAR score; HP:0002643 Neonatal respiratory distress; HP:0008872 Feeding difficulties in infancy; HP:0011471 Gastrostomy tube feeding in infancy; HP:0001319 Neonatal hypotonia; HP:0030746 Intraventricular hemorrhage; HP:0001518 Small for gestational age; HP:0000252 Postnatal microcephaly; HP:0000369 Low-set ears; HP:0000486 Strabismus; HP:0000545 Myopia; HP:0000587 Abnormality of the optic nerve; HP:0001999 Abnormal facial shape; HP:0010808 Protruding tongue; HP:0012443 Abnormality of brain morphology; HP:0033725 Thin corpus callosum; HP:0002518 Abnormal periventricular white matter morphology; HP:0001263 Global developmental delay; HP:0002421 Poor head control; HP:0001344 Absent speech; HP:0002121 Generalized non-motor (absence) seizure; HP:0001276 Hypertonia; HP:0001332 Dystonia; HP:0100660 Dyskinesia; HP:0001627 Abnormal heart morphology; HP:0001631 Atrial septal defect; HP:0001707 Abnormal right ventricle morphology; HP:0002020 Gastroesophageal reflux; HP:0002019 Constipation; HP:0002360 Sleep disturbance; HP:0010557 Overlapping fingers; HP:0001845 Overlapping toes; HP:0002205 Recurrent respiratory infections	CMA, WGS trio	SCV005091971	NM_003590.5(*CUL3*): c.2246T>C (p.Ile749Thr)	Likely pathogenic	The p.Ile749Thr variant was found de novo in a child with neurodevelopmental disorder with autism and seizures. (PS2, PM2, PP3.)	Neurodevelopmental disorder with or without autism and seizures (OMIM:619239) (AD)

Table 1 (continued) | Clinical characteristics of the patients diagnosed during the first Undiagnosed Hackathon and the variants identified

Patient ID, age, gender and country of origin	HPO terms	Genetic investigations prior to the Undiagnosed Hackathon	ClinVar SCV	HGVS variant description	Variant classification	Classification criteria according to ACMG guidelines, 2015	Diagnosis (OMIM)
HACK0008 4-year-old male Pakistan	HP:0001558 Decreased fetal movement; HP:0001511 Intrauterine growth retardation; HP:0002643 Neonatal respiratory distress; HP:0008872 Feeding difficulties in infancy; HP:0001319 Neonatal hypotonia; HP:0001518 Small for gestational age; HP:0000707 Abnormality of the nervous system; HP:0002194 Delayed gross motor development; HP:0001263 Global developmental delay; HP:0001344 Absent speech; HP:0001252 Hypotonia; HP:0001324 Muscle weakness; HP:0003011 Abnormality of the musculature; HP:0002803 Congenital contracture; HP:0001883 Talipes; HP:0008110 Equinovarus deformity; HP:0006532 Recurrent pneumonia	WES singleton	SCV005091972	NM_002180.3(*IGHMBP2*): c.1328G>A (p.Arg443His)	Likely pathogenic	This sequence change (p.Arg443His) was found in homozygous state in a patient with spinal muscular atrophy with respiratory distress. ClinVar contains an entry for this variant (Variation ID: 863993). In silico prediction indicates that this missense variant is expected to disrupt IGHMBP2 protein function. The same amino acid is reported as pathogenic (p.Arg443Cys; Variation ID: 617575). (PP3, PM2, PM5.)	Spinal muscular atrophy with respiratory distress type 1 (OMIM:604320) (AR)
HACK0013 3-year-old female Congo	HP:0025116 Fetal distress; HP:0030917 Low APGAR score; HP:0002643 Neonatal respiratory distress; HP:0008872 Feeding difficulties in infancy; HP:0032807 Neonatal seizure; HP:0003498 Disproportionate short stature; HP:0001999 Abnormal facial shape; HP:0000347 Micrognathia; HP:0011220 Prominent forehead; HP:0000286 Epicanthus; HP:0010938 Abnormality of the external nose; HP:0012471 Thick vermilion border; HP:0000343 Long philtrum; HP:0000163 Abnormal oral cavity morphology; HP:0005105 Abnormal nasal morphology; HP:0000369 Low-set ears; HP:0000929 Abnormal skull; HP:0000470 Short neck; HP:0000765 Abnormal thorax morphology; HP:0000707 Abnormality of the nervous system; HP:0002194 Delayed gross motor development; HP:0001263 Global developmental delay; HP:0007018 Attention deficit hyperactivity disorder; HP:0100716 Self-injurious behavior; HP:0000718 Aggressive behavior; HP:0002465 Poor speech; HP:0000750 Delayed speech and language development; HP:0001250 Seizure; HP:0001156 Brachydactyly; HP:0001831 Brachydactyly of the foot; HP:0001845 Overlapping toes; HP:0001627 Abnormal heart morphology; HP:0001000 Abnormality of skin pigmentation; HP:0001595 Abnormal hair morphology; HP:0001597 Abnormality of the nails; HP:0100790 Hernia	None	SCV005091973	NM_005343.4(*HRAS*): c.35G>C (p.Gly12Ala)	Pathogenic	This variant was found de novo in a child with Costello syndrome. It disrupts the p.Gly12 amino acid residue in *HRAS*. Other variants that disrupt this residue have been determined to be pathogenic (PMID: 16170316, 20979192, 21834037, 21850009, 22317973, 23751039). Experimental studies have shown that this missense change affects HRAS function (PMID: 17979197, 21850009, 24224811). In silico prediction indicates that this missense variant is expected to disrupt HRAS function. This missense change has been observed in individuals with Costello syndrome (PMID: 16170316, 16372351, 16443854, 16835863, 17601930, 18042262, 21850009, 22420426, 28027064). (PS3, PS1, PS2, PM1, PM2, PP3.)	Costello syndrome (OMIM:218040) (AD)

AD, autosomal dominant; AR, autosomal recessive; ClinVar SCV, accession number assigned by ClinVar to the submitted interpretation of the variant–condition pair; CMA, chromosomal microarray; WES, whole-exome sequencing; WGS, whole-genome sequencing.

Holding future Undiagnosed Hackathons would stimulate global collaboration and start-ups of focused working groups aiming to accelerate solutions in rare disease diagnostics, such as tools for multi-omics data analysis, advanced phenotyping tools, streamlined variant assessment, data-sharing frameworks and large-scale gene discovery programs, aided by artificial intelligence and machine learning. The resources generated by the event can then be used to advance research, for technical development and to improve precision diagnostics, prevention, treatment and care (Fig. 1).

In summary, the Undiagnosed Hackathon has presented an inspiring model of multidisciplinary global collaboration and patient partnership and has advanced the limits of diagnostics for undiagnosed rare diseases. Furthermore, the event has opened doors for future initiatives that align with the goal of the International Rare Diseases Research Consortium (IRDiRC) that undiagnosed individuals have access to a globally coordinated diagnostic and research pipeline[7]. The lessons learned and the successes achieved indicate that this format holds substantial potential toward achieving health equity for patients worldwide and a future in which undiagnosed diseases have become a thing of the past.

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References

1. Nguengang Wakap, S. et al. *Eur. J. Hum. Genet.* **28**, 165–173 (2020).
2. Wright, C. F. et al. *N. Engl. J. Med.* **388**, 1559–1571 (2023).
3. Edsjo, A. et al. *Camb. Prism. Precis. Med.* **1**, e15 (2023).
4. Baynam, G., Gomez, R. & Jain, R. *Front. Genet.* **15**, 1335768 (2024).
5. Sciascia, S. et al. *Front. Public Health* **11**, 1248260 (2023).
6. Hoytema van Konijnenburg, E. M. M. et al. *Orphanet J. Rare Dis.* **16**, 170 (2021).
7. Nabbout, R. et al. *Orphanet J. Rare Dis.* **18**, 109 (2023).
8. Rubinstein, Y. R. et al. *JAMA Open* **3**, 472–486 (2020).
9. Zurek, B. et al. *Eur. J. Hum. Genet.* **29**, 1325–1331 (2021).
10. Palmer, E. E. et al. *NPJ Genom. Med.* **9**, 37 (2024).
11. Taruscio, D. et al. *Mol. Genet. Metab.* **129**, 243–254 (2020).
12. Montano, C. et al. *J. Inherit. Metab. Dis.* **45**, 907–918 (2022).
13. Richards, S. et al. *Genet. Med.* **17**, 405–424 (2015).
14. Taruscio, D. & Gahl, W. A. *Nat. Rev. Dis. Primers* **10**, 13 (2024).
15. Hay, G. J. et al. *Front. Pediatr.* **8**, 582 (2020).

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Author contributions

H.C., M. Cederroth, A.N., A.M.D.V. and O.B. conceptualized and designed the Undiagnosed Hackathon. Biological samples and phenotype data were collected by A.M.D.V., A.N., H.C., M. Cederroth, R.Y., V.S., S.A.W., Y. Alanay, L.D.B., S.K., A. Lumaka and R.D.P. Samples were processed and analyzed under the coordination of A.M.D.V, F.T., K.E., M. Ek, H.T., A.J., D.N., J.E., K.B.S, I.H., J.N. A. Lindstrand, A.N. and V.W. All authors participated in the analysis and interpretation of the data during the event and through regular collaborative discussions meetings after the event. The manuscript was drafted by A.M.D.V, H.C., M. Cederroth, F.T., A. Lindstrand, G.B., E.E.P., L.D.B., O.B. and A.N., with significant contributions and critical feedback from all authors. A.N., H.C. and M. Cederroth secured funding for the event. All authors have reviewed and approved the final version of the manuscript.

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