Supplementary appendix

This appendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

Web Extra Material

Retrospective Analysis of Diagnostic and Clinical Findings among Critically Ill Infants Receiving Rapid Whole Genome Sequencing for Identification of Mendelian Disorders

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Additional Results

1. Quantitative comparison of clinical features of genetic diseases in infants with classical disease descriptions.

In infants with STATseq diagnoses, the degree of overlap between the classical clinical features of the disease and features that were noted was assessed. Nomination forms and medical records were reviewed by a clinical geneticist to generate phenotypic terms. HPO terms for these were mapped to genetic diseases with the Phenomizer (appendix, Table S1).\(^3\,36\,38\) The rank of the diagnosis in the genetic disease compendium indicated concordance of actual and expected presentations (appendix, Table S1). Among 19 infants whose genetic diagnosis was in the Phenomizer database, the mean rank was 806 (SD 1269; median 181, range 1–4509; appendix, Table S1). By contrast, the mean rank among 32 older children with neurodevelopmental disorders diagnosed by use of genomic sequencing was 279 (SD 425; median 128, range 1–1740; appendix, Table S5).\(^30\)

2. Additional examples of infants where STATseq diagnoses were associated with substantial changes in management and subsequent favourable outcomes:

i. CMH586

CMH586 was admitted on DOL 63 for failure to thrive (weight 5\(^{th}\) percentile for a 2-week old, length 6\(^{th}\) percentile, head circumference 15\(^{th}\) percentile) with lactic acidosis, hypoglycemia, and abnormal liver function. Intravenous dextrose increased the lactic acid. Ketosis was minimal and the ratio of lactate to pyruvate was normal. The empiric diagnosis was pyruvate dehydrogenase complex deficiency, and a modified ketogenic diet was started. STATseq identified reversible cytochrome C oxidase deficiency with a maternally inherited homoplasmic mitochondrial mutation. This diagnosis conferred a highly favorable long-term prognosis and, thus, changed the clinical impression such that intensive interventions were in fact indicated had the acute clinical course deteriorated. The ketogenic diet was unnecessary and was discontinued. She is now 20 months old and has normal growth, weight, and age-appropriate development.

ii. CMH680

CMH680 was diagnosed with early infantile epileptic encephalopathy, type 11, resulting in institution of a ketogenic diet and a change in anti-epileptic drug. She is now 19 months old, at home, and continues to have seizures but had improvement in electroencephalograms following the changes in diet and anticonvulsant.

3. Additional Tables S1 – S5

Table S1: HPO terms corresponding to the principal clinical features of study infants and Phenomizer rank and P-value of molecular diagnoses identified herein.

Average rank was 806. Median rank was 181.
<table>
<thead>
<tr>
<th>Patient ID</th>
<th>Signs and Symptoms</th>
<th>HPO #</th>
<th>HPO Term</th>
<th>Diagnoses</th>
<th>Gene</th>
<th>Rank</th>
<th>P-value</th>
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### Table S3: Standard genetic tests performed on enrolled infants.

Legend: *Targeted Gene Sequencing and Custom Analysis (TaGSCAN) is a targeted screening panel covering coding regions of 572 genes known to cause severe diseases with childhood onset. **CHD7 and SEMA3E gene sequence analysis for CHARGE Syndrome were ordered, but cancelled upon return of STATseq diagnosis. D, diagnostic. N, not diagnostic. NGS, next-generation sequencing.*
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Table S4: Presentations, genetic diagnoses, inheritance patterns, and detailed evidence for variant pathogenicity in the cohort\textsuperscript{45}.

Legend: **Paternal sample unavailable; ***Paternally inherited variant with presumed somatic loss of maternal allele function or paternal UPD; Abbreviations and symbols: n.a., not applicable; Y, yes; N, no; £, variant was unique to this family (or patient) in the internal CM-KC variant database; CTL, control; AR, autosomal recessive; MAF, minor allele frequency; db, variant allele frequency database; CMH, CM-KC internal variant warehouse; 1KG, One thousand genomes project database/dbSNP; EVS, exome variant server database.

Interpretation criteria\textsuperscript{45}: P = pathogenic, LP = likely pathogenic, VUS = variant of unknown significance. ACMG criteria: Pathogenic= 1 Stand-Alone OR 2 Strong OR 1 Strong + > 3 Supporting evidence items; Likely-Pathogenic= 1 Strong + 2 supporting OR 4 Supporting items of evidence. Minor allele frequency cutoff guidance: Autosomal dominant MAF <0.4%; Autosomal Recessive MAF <1% Pathogenicity support: B = benign; T = tolerated; D = Damaging/Deleterious/Disease Causing; nk = not known; P = benign polymorphism; PD = probably damaging; SD = possibly damaging.
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<td>Assumed De Novo**</td>
<td>Co-Segregation with disease</td>
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Table S5: Clinical features of control children receiving genomic sequencing for diagnosis of neurodevelopmental disabilities and Phenomizer ranking of diagnoses.

Average rank was 279. Median rank was 128.
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