

Supplementary Information File

An automated 13.5 hour system for scalable diagnosis and acute management guidance for genetic diseases

Mallory J. Owen, Sebastien Lefebvre, Christian Hansen, Chris M. Kunard, David P. Dimmock, Laurie D. Smith, Gunter Scharer, Rebecca Mardach, Mary J. Willis, Annette Feigenbaum, Anna-Kaisa Niemi, Yan Ding, Luca Van Der Kraan, Katarzyna Ellsworth, Lucia Guidugli, Bryan R. Lajoie, Timothy K. McPhail, Shyamal S. Mehtalia, Kevin K. Chau, Yong H. Kwon, Zhanyang Zhu, Sergey Batalov, Shimul Chowdhury, Seema Rego, James Perry, Mark Speziale, Mark Nespeca, Meredith S. Wright, Martin G. Reese, Francisco M. De La Vega, Joe Azure, Erwin Frise, Charlene Son Rigby, Sandy White, Charlotte A. Hobbs, Sheldon Gilmer, Gail Knight, Albert Oriol, Jerica Lenberg, Shareef A. Nahas, Kate Perofsky, Kyu Kim, Jeanne Carroll, Nicole G. Coufal, Erica Sanford, Kristen Wigby, Jacqueline Weir, Vicki S. Thomson, Louise Fraser, Seka S. Lazare, Yoon H. Shin, Haiying Grunenwald, Richard Lee, David Jones, Duke Tran, Andrew Gross, Patrick Daigle, Anne Case, Marisa Lue, James A. Richardson, John Reynders, Thomas Defay, Kevin P. Hall, Narayanan Veeraraghavan, Stephen F. Kingsmore.

Supplementary Tables

Table S1. Precision and recall of phenotypic features extracted by CNLP from EHRs in 10 children with genetic diseases.

Table S2. Characteristics of 4 retrospective cases used to test performance of the 13.5 hour automated sequencing and interpretation pipeline.

Table S3. Analytic performance of 3 automated interpretation software systems, MOON (InVita), GEM (Fabric Genomics) and Trusight Software Suite (Illumina), in 4 retrospective cases and one prospective case.

Table S4. Concordance and interventions reviewed, retained, and deleted for 15 GTRx pilot genes that underwent independent review by five expert biochemical geneticists.

Table S5. Fields used in the curation of gene-condition associations.

Table S6. Results from a survey of nine clinicians on the user interface of GTRx.

Supplementary Data

Supplementary Data 1. 563 genetic disorders associated with 357 genes identified as presenting in the pediatric population and having available treatment. Abbreviations: NBS, Newborn Screening. ORPHA., Orphanet. DEF., deficiency or deficient. HERED., hereditary. SUSC., susceptibility. CONG., congenital. AR, autosomal recessive. AD, autosomal dominant. FAM., familial. SYN., syndrome. INF., infancy. -, negative. W/W, with or without. GEN., generalized. NEO., neonatal. PROG., progressive. XL, X-linked. &, and. ASSOC W., associated with. SEV., severe. AUT., autosomal. D.T., due to. COMP., complementation group. COMB., combined. ABN., abnormalities or anomalies. +, POSITIVE. DIS., disease, or disorder.

Supplemental Data 2. Variables included in the RedCap instance used to review interventions pulled by automatic and manual curation.

Supplemental Data 3. The 8,889 interventions curated, reviewed, and retained or rejected in 563 genetic disorders. Concordance value N/A signifies no secondary review performed for this set of interventions.

Supplementary Figures

Figure S1: Screenshot from Genome-To-Treatment (GTRx) for Timothy Syndrome-*CACNA1C*

Figure S2: Screenshot of Acute Treatment Detail from Genome-To-Treatment (GTRx) for Timothy Syndrome-*CACNA1C*

Figure S3. Screenshot from GTRx for Hereditary Fructose Intolerance-*ALDOB*

Figure S4. Genome-To-Treatment (GTRx) RedCap review system for Timothy Syndrome-*CACNA1C*. Select Interventions For Review page.

Figure S5. Genome-To-Treatment (GTRx) RedCap review system for Timothy Syndrome-*CACNA1C*. Intervention / Treatment page for Propanolol.

Figure S6. Genome-To-Treatment (GTRx) RedCap review system for Timothy Syndrome-*CACNA1C*. List Of Disease Treatment Publications page.

Figure S7. Genome-To-Treatment (GTRx) RedCap review system for Timothy Syndrome-*CACNA1C*. Secondary Review page.

Supplementary Methods

GTRx General Principles for Intervention Review and Adjudication

Table S1. Precision and recall of phenotypic features extracted by NLP from EHRs in 10 children with genetic diseases. Precision=tp/tp+fp. Recall=tp/tp+fn. Abbreviations: EIEE: Early Infantile Epileptic Encephalopathy; AD: Autosomal Dominant; AR: Autosomal Recessive; DN: de novo; P: Pathogenic; LP: Likely Pathogenic; S: Singleton; T: Trio; I: Inherited; U: undetermined; OMIM: Online Mendelian Inheritance in Man; CF: Clinical Feature; Inh: Inheritance; n.a.: not applicable; WES: whole exome sequencing.

Family	S or T	WES or WGS	Disease	Affected Gene	MIM ID	Inh	DN or I	Variant 1 (V1)	Variant 2 (V2)	V1 P/ LP	V2 P/ LP	DOL NLP extract	Sex	Consanguinity	NLP Features	NLP Precision	NLP Recall
201	T	WES	Prader Willi Syndrome	15q11-q13 del	176270	AD	DN	Chr15:23684685-26108259del	n.a.	P		4	♀	U	89	0.53	0.95
205	T	WGS	Dursun Syndrome	<i>G6CP3</i>	612541	AR	I	c.207dupC, p.Ile70Hisfs	c.199_218+1delCTCAACCTCATCTTCAAGTGG	P	P	2	♂	No	94	0.93	0.95
213	S	WGS	Visceral Heterotaxy 5	<i>NODAL</i>	270100	AD	I	c.778G>A, p.Gly260Arg	n.a.		LP	3	♂	U	89	0.90	0.98
233	T	WGS	Tuberous Sclerosis 1	<i>TSC1</i>	191100	AD	DN	c.1498C>T, p.Arg500Ter	n.a.		P	5	♀	No	167	0.57	0.95
243	T	WGS	Pyridoxine dependent seizures	<i>ALDH7A1</i>	266100	AR	I	c.328C>T, p.Arg110Ter	c.1279G>C, p.Glu427Gln	P	P	6	♂	No	36	0.97	0.50
6094	T	WGS	Argininosuccinic aciduria	<i>ASL</i>	207900	AR	I	c.706C>T, p.Arg236Trp	c.706C>T, p.Arg236Trp	P	P	4	♀	Yes	55	0.85	0.87
6098	T	WGS	Gaucher disease	<i>GBA</i>	230800	AR	I	c.1503C>G, p.Asn501Lys	p.Leu483Pro		LP P	215	♀	No	112	0.92	0.94
6108	T	WGS	Tuberous Sclerosis 2	<i>TSC2</i>	613254	AD	DN	c.935_936delTC, p.Leu312Glnfs	n.a.		P	4	♂	No	86	0.76	0.98
7003	T	WGS	EIEE6	<i>SCN1A</i>	607208	AD	DN	p.Met1852Thr	n.a.		P	424	♂	U	67	0.81	0.93
7004	T	WGS	Hypertrophic cardiomyopathy 1	<i>MYH7</i>	192600	AD	I	c.746G>A, p.Arg249Gln	n.a.		P	5171	♂	U	99	0.68	0.96
Average															89.4	0.79	0.90
Standard Deviation															35.3	0.15	0.14

Table S2. Characteristics of four retrospective and three prospective cases used to test performance of the 13.5-hour automated sequencing and interpretation pipeline (Table 1, Figure 4). Abbreviations: R: Retrospective; Pr: Prospective; AD: Autosomal Dominant; DN: de novo; P: Pathogenic; LP: Likely Pathogenic; M: Male; F: Female; S: Singleton; T: Trio; Inh: Inherited; XL: X linked; Het: Heterozygous; Hom: Homozygous; Hem: Hemizygous; OMIM: Online Mendelian Inheritance in Man; n.a.: not applicable; n.k.: not known; MT: mitochondrial; HP: heteroplasmic; D: Duo.

Analysis	Subject ID	S or T	Disease	Gene	OMIM ID	Inheritance	Zygoty	de novo or inherited	Variant 1 (V1)	Variant 2 (V2)	V1 P/LP	V2 P/LP	Age at enrollment (days)	Sex	Parents Consanguinous
Retro-spective	AG928	S	Hereditary Fructose Intolerance	<i>ALDOB</i>	229600	AR	Het	n.k	c.448G>C, p.Ala150Pro	c.524C>A, p.Ala175Asp	P	P	107	M	N
	AG366	S	Ornithine Transcarbamylase Deficiency	<i>OTC</i>	311250	XL	Hem	<i>De Novo</i>	c.275G>A, p.Arg92Gln	n.a.	P	na	5	M	N
	AF414	S	Propionic Acidemia	<i>PCCA</i>	606054	AR	Hom	n.k	c.1899+4_1899+7del	n.a.	LP	na	4	F	N
	AI003	T	Developmental and epileptic encephalopathy 11	<i>SCN2A</i>	613721	AD	Het	<i>De Novo</i>	c.4437G>C, p.Gln1479His	n.a.	LP	na	7	F	N
Pro-spective	AH638	T	Thiamine metabolism dysfunction syndrome 2	<i>SLC19A3</i>	607483	AR	Hom	Inh	c.597dup, H200fs	n.a.	P	na	42	M	Y
	CSD59F	D	Leigh syndrome	<i>MT-ATP6</i>	256000	MT	HP	<i>De Novo</i>	m.8993T>C, p.Leu156Pro	n.a.	P	na	6	M	N
	CSD709	S	Geleophysic dysplasia	<i>ADAMTSL2</i>	231050	AR	Het	Inh	c.338G>T, p.Arg113Leu	c.1851C>A, p.Cys617Ter	P	LP	1	M	N

Table S3. Analytic performance of 3 automated interpretation software systems (MOON (InVitae), GEM (Fabric Genomics) and Trusight Software Suite (Illumina)) in 4 retrospective cases and one prospective case. *Includes processing time for DRAGEN v3.7. Abbreviations: SNV: single nucleotide variant; SV: structural variant; CNV: copy number variant.

Case Number	AG928	AI115	AI148	AI185	AH638	Average
Run	1020	1204	1208	1218	1026	
Type of case		Retrospective			Prospective	
Diagnosis	<i>ALDOB</i>	<i>OTC</i>	<i>PCCA</i>	<i>SCN2A</i>	<i>SLC19A3</i>	
MOON (InVitae)						
Rank of correct diagnosis	1	1	1	1	1	1
SNVs	6	7	9	4	10	7.2
SV/CNVs	20	1	11	8	0	8
Total	26	8	20	12	11	15.4
Time to provisional diagnosis (min)	9	10	12	10	10	10.2
GEM (Fabric Genomics)						
Rank of correct diagnosis	3	1	1	4	1	2
Ranked variants (including SV/CNVs)	5	6	5	16	8	8
Time to provisional diagnosis (min)	39	43	44	40	48	42.8
Trusight Software Suite (Illumina)						
Rank of correct diagnosis	1	1	1	1	1	1
SNVs	5	2	2	5	15	5.8
SV/CNVs	0	0	0	0	0	0
Total	5	2	2	5	15	5.8
Time to provisional diagnosis (min)*	213	230	178	276	220	223.4

Table S4. Concordance and interventions reviewed, retained and deleted in the 15 GTRx pilot genes that underwent independent review by 5 expert biochemical geneticists.

Condition	OMIM ID	Gene Affected	Total Interventions Curated	Interventions with concordant reviews	Concordance	Interventions retained after adjudication	Original interventions retained	Interventions deleted	Interventions deleted
Timothy Syndrome	601005	<i>CACNA1C</i>	19	14	74%	8	42%	11	58%
Primary aldosteronism, seizures, & neurologic abnormalities	615474	<i>CACNA1D</i>	6	4	67%	5	83%	1	17%
Carnitine Acylcarnitine Translocase Deficiency	212138	<i>SLC25A20</i>	8	6	75%	8	100%	0	0%
Maple Syrup Urine Disease	248600	<i>DBT</i>	14	4	29%	9	64%	5	36%
Congenital Myasthenic Syndrome	614750	<i>DPAGT1</i>	12	2	17%	1	8%	11	92%
Glycogen Storage Disease III	232400	<i>AGL</i>	5	1	20%	3	60%	2	40%
Tyrosinemia Type 1	276700	<i>FAH</i>	6	4	67%	3	50%	3	50%
Fructose 1,6 Bisphosphatase Deficiency	229700	<i>FBP1</i>	6	4	67%	4	67%	2	33%
Glycogen Storage Disease 1a	232200	<i>G6PC</i>	21	7	33%	6	29%	15	71%
Glycogen Storage Disease 1b	232220	<i>SLC37A4</i>	15	4	27%	5	33%	10	67%
Glycogen Storage Disease II	232300	<i>GAA</i>	24	17	71%	7	29%	17	71%
Galactosemia II	230200	<i>GALK1</i>	1	1	100%	1	100%	0	0%
Hereditary Fructose Intolerance	229600	<i>ALDOB</i>	2	1	50%	1	50%	1	50%
Ornithine Transcarbamylase Deficiency	311250	<i>OTC</i>	22	10	45%	13	59%	9	41%
Propionic Acidemia	606054	<i>PCCA</i>	29	15	52%	14	48%	15	52%
Average			12.7	6.3	52.8%	5.9	54.9%	6.8	45.1%
Standard Deviation			8.7	5.3	24.1%	4.1	25.9%	6.0	25.9%

Table S5. Fields used in the curation of gene-condition associations.

Responsible entity	Field	Description	Guidance Provided
Automated data pull	HGNC gene id		
Automated data pull	HGNC gene symbol		
Automated data pull	condition_id	OMIM ID if no OMIM use Orphanet ID. OMIM:<ID> or ORPHA:<ID>	
Automated data pull	condition_name	OMIM name if no OMIM use Orphanet name	
Curator	intervention_excerpt	abbreviation of excerpt or excerpt from the evidence source that mentions the acute case intervention	Focus on pediatric acute cases and if little evidence expand to human acute cases then to human cases. No animal models.
Curator	intervention_type	possible values = medicine, surgery, device, diet, other	
Curator	drug_name	molecule, drug, formulation	
Curator	drugbank_id	DrugBank ID	
Curator	intervention_evidence_PMIID	list of PubMed ids	supporting evidence of the intervention for the given gene-condition
Curator	category_of_evidence	list of value from (1a, 1b, 2a, 2b, 2c, 3a, 3b, 3c, 4, 5)	Category of Evidence supporting clinical utility of intervention
Curator	effectiveness_of_intervention	C = Curative, E = Effective, or A = Amerliorative	from www.ncbi.nlm.nih.gov/pubmed/10037645

Table S6. Results of nine clinician surveys of perceptions of GTRx.

SURVEY QUESTION (10 POINT LIKERT SCALE, 1=LOWEST, 10=HIGHEST)	MEDIAN RESPONSE	MINIMUM	MAXIMUM
Q1. WOULD YOU USE THIS WEBSITE AS A CLINICIAN?	9	3	10
Q2. HOW EASY IS THE WEBSITE TO USE?	9	8	10
Q3. HOW EASY IS IT TO FIND THE INFORMATION YOU'D LIKE TO SEE?	9	5	10
Q4. HOW USEFUL IS THE INFORMATION PROVIDED?	6	5	10
SURVEY QUESTION (5 POINT LIKERT SCALE, 1=LOWEST, 5=HIGHEST)	Median Response	Minimum	Maximum
Q5. OVERALL, HOW WELL DOES GTRX MEET YOUR NEEDS?	3 (Somewhat)	2 (Not so well)	4 (Very)
Q6. HOW VISUALLY APPEALING IS GTRX?	4 (Very)	3 (Somewhat)	5 (Extremely)
Q7. HOW EASY IS IT TO UNDERSTAND THE INFORMATION ON THE WEBSITE?	4 (Very)	3 (Somewhat)	5 (Extremely)

Supplementary Figures

GTRx Index of Conditions Index of Genes About GTRx ACELION Rady Children's Institute

Contents

- Condition
- Gene Information
- Interventions
- Clinical Summary
- References
- HPO Terms
- Feedback

TIMOTHY SYNDROME

Alternate Name(s)
TIMOTHY SYNDROME
BRUGADA SYNDROME 3
LONG QT SYNDROME 8

Incidence
Timothy syndrome is a rare condition; fewer than 100 people with this disorder have been reported worldwide.

Inheritance
Autosomal dominant

WARNING: HIGH RISK OF HYPOGLYCEMIA DURING GENERAL ANESTHESIA.

Subspecialist Input Required
Cardiology, Anesthesiology
Cardiology - Electrophysiology

Gene Information SEQUENCE VIEWER

CACNA1C NCBI GENE
Location: 12p13.33
Gene name: calcium voltage-gated channel subunit alpha1 C GHR

Recommended Acute Treatments and Interventions COLLAPSE ALL

Interventions that are appropriate for acute management of this diagnosis in an infant or child in an intensive care unit.

<p>> Beta-blockers Must be started within Hours</p> <p style="text-align: right;">COMMENT</p>
<p>> Atenolol, Nadolol Must be started within Hours</p> <p style="text-align: right;">COMMENT</p>
<p>> Lidocaine Must be started within Hours</p> <p style="text-align: right;">COMMENT</p>
<p>> IV esmolol Must be started within Hours</p> <p style="text-align: right;">COMMENT</p>
<p>> Left cervical sympathetic denervation Must be started within Days or Weeks, Years Unsuitable for Neonates under 29 days old</p> <p style="text-align: right;">COMMENT</p>
<p>> Mexiletine Must be started within Days or Weeks</p> <p style="text-align: right;">COMMENT</p>
<p>> Permanent pacemaker Must be started within Days or Weeks, Years</p> <p style="text-align: right;">COMMENT</p>
<p>> Magnesium Must be started within Hours</p> <p style="text-align: right;">COMMENT</p>
<p>> Propranolol Must be started within Hours Contraindications</p> <p style="text-align: right;">COMMENT</p>
<p>> Implantable cardioverter defibrillator Must be started within Days or Weeks, Years</p> <p style="text-align: right;">COMMENT</p>

Authoritative Information Resources

- GHR
- Orphanet
- GARD
- OMIM
- GeneReviews

Contents

- Condition
- Gene Information
- Interventions
- Clinical Summary
- References
- HPO Terms
- Feedback

Clinical Summary

TIMOTHY SYNDROME

Timothy syndrome is a rare disorder that primarily affects the heart but can affect many other areas of the body, including the fingers and toes, teeth, nervous system, and immune system. The severity of this condition varies among affected individuals, although it is often life-threatening due to the heart problems. Timothy syndrome is characterized by a heart condition called long QT syndrome, which causes the heart (cardiac) muscle to take longer than usual to recharge between beats. This abnormality in the heart's electrical system can cause severe abnormalities of the heart rhythm (arrhythmias), which can lead to sudden death. Some people with Timothy syndrome are also born with structural heart defects (cardiomyopathy) that affect the heart's ability to pump blood effectively. As a result of these serious heart problems, many people with Timothy syndrome live only into childhood. In about 80 percent of cases of Timothy syndrome, the cause of death is a severe form of arrhythmia called ventricular tachycardia, in which the lower chambers of the heart (the ventricles) beat abnormally fast, often leading to cardiac arrest and sudden death. Timothy syndrome is also characterized by webbing or fusion of the skin between some fingers or toes (cutaneous syndactyly). About half of affected people have distinctive facial features such as a flattened nasal bridge, low-set ears, a small upper jaw, and a thin upper lip. Children with this condition have small, misplaced teeth and frequent cavities (dental caries). Additional signs and symptoms of Timothy syndrome can include baldness at birth, frequent infections, episodes of low blood sugar (hypoglycemia), and an abnormally low body temperature (hypothermia). Researchers have found that many children with Timothy syndrome have the characteristic features of autism or similar conditions known as autistic spectrum disorders. Affected children tend to have impaired communication and socialization skills, as well as delayed development of speech and language. Other nervous system abnormalities that can occur in Timothy syndrome include intellectual disability and recurrent seizures (epilepsy); some affected individuals have photosensitive epilepsy, in which seizures are triggered by flashing lights.

> **List of References**

> **Human Phenotype Ontology (HPO) Terms Associated with TIMOTHY SYNDROME** GARD HPO TERMS

Authoritative Information Resources

- GHR
- Orphanet
- GARD
- OMIM
- GeneReviews

GTRx is provided for research use only and is not intended for clinical use. It has not been approved by the FDA. Users of this tool retain all responsibility for any medical decision-making including diagnosis, treatment and case management.

Figure S1: Screenshot from Genome-To-Treatment (GTRx) for Timothy Syndrome-CACNA1C

Recommended Acute Treatments and Interventions

Interventions that are appropriate for acute management of this diagnosis in an infant or child in an intensive care unit.

<p>> Beta-blockers Must be started within Hours</p> <p style="text-align: right;">COMMENT</p>											
<p>> Atenolol, Nadolol Must be started within Hours</p> <p style="text-align: right;">COMMENT</p>											
<p>∨ Lidocaine Must be started within Hours</p> <p>Considered for acute anti-arrhythmic therapy only</p> <table border="0"> <tr> <td>How long after diagnosis does this intervention need to be started?</td> <td>Hours</td> </tr> <tr> <td>Age group in which this intervention may be started</td> <td>Neonate, Infant, Child</td> </tr> <tr> <td>Are there groups in which this intervention is contraindicated?</td> <td>No</td> </tr> <tr> <td>What is the level of evidence available for this intervention?</td> <td>Case report(s)</td> </tr> <tr> <td>What is the efficacy of this intervention?</td> <td>Effective / Ameliorative</td> </tr> </table> <p style="text-align: right;">COMMENT</p>		How long after diagnosis does this intervention need to be started?	Hours	Age group in which this intervention may be started	Neonate, Infant, Child	Are there groups in which this intervention is contraindicated?	No	What is the level of evidence available for this intervention?	Case report(s)	What is the efficacy of this intervention?	Effective / Ameliorative
How long after diagnosis does this intervention need to be started?	Hours										
Age group in which this intervention may be started	Neonate, Infant, Child										
Are there groups in which this intervention is contraindicated?	No										
What is the level of evidence available for this intervention?	Case report(s)										
What is the efficacy of this intervention?	Effective / Ameliorative										
<p>∨ IV esmolol Must be started within Hours</p> <p>Beta blockers are the mainstay of treatment. Expert consensus is that nadolol is the best beta blocker for use in TS, with propranolol second best. Specific beta blocker use depends on age, acuity and route of administration.</p> <table border="0"> <tr> <td>How long after diagnosis does this intervention need to be started?</td> <td>Hours</td> </tr> <tr> <td>Age group in which this intervention may be started</td> <td>Neonate, Infant, Child</td> </tr> <tr> <td>Are there groups in which this intervention is contraindicated?</td> <td>No</td> </tr> <tr> <td>What is the level of evidence available for this intervention?</td> <td>Case report(s)</td> </tr> <tr> <td>What is the efficacy of this intervention?</td> <td>Effective / Ameliorative</td> </tr> </table> <p style="text-align: right;">COMMENT</p>		How long after diagnosis does this intervention need to be started?	Hours	Age group in which this intervention may be started	Neonate, Infant, Child	Are there groups in which this intervention is contraindicated?	No	What is the level of evidence available for this intervention?	Case report(s)	What is the efficacy of this intervention?	Effective / Ameliorative
How long after diagnosis does this intervention need to be started?	Hours										
Age group in which this intervention may be started	Neonate, Infant, Child										
Are there groups in which this intervention is contraindicated?	No										
What is the level of evidence available for this intervention?	Case report(s)										
What is the efficacy of this intervention?	Effective / Ameliorative										
<p>∨ Left cervical sympathetic denervation Must be started within Days or Weeks, Years Unsuitable for Neonates under 29 days old</p> <table border="0"> <tr> <td>How long after diagnosis does this intervention need to be started?</td> <td>Days or Weeks, Years</td> </tr> <tr> <td>Age group in which this intervention may be started</td> <td>Infant, Child</td> </tr> <tr> <td>Are there groups in which this intervention is contraindicated?</td> <td>No</td> </tr> <tr> <td>What is the level of evidence available for this intervention?</td> <td>Case report(s)</td> </tr> <tr> <td>What is the efficacy of this intervention?</td> <td>Effective / Ameliorative</td> </tr> </table> <p style="text-align: right;">COMMENT</p>		How long after diagnosis does this intervention need to be started?	Days or Weeks, Years	Age group in which this intervention may be started	Infant, Child	Are there groups in which this intervention is contraindicated?	No	What is the level of evidence available for this intervention?	Case report(s)	What is the efficacy of this intervention?	Effective / Ameliorative
How long after diagnosis does this intervention need to be started?	Days or Weeks, Years										
Age group in which this intervention may be started	Infant, Child										
Are there groups in which this intervention is contraindicated?	No										
What is the level of evidence available for this intervention?	Case report(s)										
What is the efficacy of this intervention?	Effective / Ameliorative										
<p>∨ Mexiletine Must be started within Days or Weeks</p> <p>Beta-blockers remain the mainstay of treatment, but mexiletine is an additional option for patients who continue to experience cardiac events while on beta-blockade.</p> <table border="0"> <tr> <td>How long after diagnosis does this intervention need to be started?</td> <td>Days or Weeks</td> </tr> <tr> <td>Age group in which this intervention may be started</td> <td>Neonate, Infant, Child</td> </tr> <tr> <td>Are there groups in which this intervention is contraindicated?</td> <td>No</td> </tr> <tr> <td>What is the level of evidence available for this intervention?</td> <td>Cohort study or studies</td> </tr> <tr> <td>What is the efficacy of this intervention?</td> <td>Effective / Ameliorative</td> </tr> </table> <p style="text-align: right;">COMMENT</p>		How long after diagnosis does this intervention need to be started?	Days or Weeks	Age group in which this intervention may be started	Neonate, Infant, Child	Are there groups in which this intervention is contraindicated?	No	What is the level of evidence available for this intervention?	Cohort study or studies	What is the efficacy of this intervention?	Effective / Ameliorative
How long after diagnosis does this intervention need to be started?	Days or Weeks										
Age group in which this intervention may be started	Neonate, Infant, Child										
Are there groups in which this intervention is contraindicated?	No										
What is the level of evidence available for this intervention?	Cohort study or studies										
What is the efficacy of this intervention?	Effective / Ameliorative										
<p>∨ Permanent pacemaker Must be started within Days or Weeks, Years</p> <table border="0"> <tr> <td>How long after diagnosis does this intervention need to be started?</td> <td>Days or Weeks, Years</td> </tr> <tr> <td>Age group in which this intervention may be started</td> <td>Neonate, Infant, Child</td> </tr> <tr> <td>Are there groups in which this intervention is contraindicated?</td> <td>No</td> </tr> <tr> <td>What is the level of evidence available for this intervention?</td> <td>Cohort study or studies</td> </tr> <tr> <td>What is the efficacy of this intervention?</td> <td>Effective / Ameliorative</td> </tr> </table> <p style="text-align: right;">COMMENT</p>		How long after diagnosis does this intervention need to be started?	Days or Weeks, Years	Age group in which this intervention may be started	Neonate, Infant, Child	Are there groups in which this intervention is contraindicated?	No	What is the level of evidence available for this intervention?	Cohort study or studies	What is the efficacy of this intervention?	Effective / Ameliorative
How long after diagnosis does this intervention need to be started?	Days or Weeks, Years										
Age group in which this intervention may be started	Neonate, Infant, Child										
Are there groups in which this intervention is contraindicated?	No										
What is the level of evidence available for this intervention?	Cohort study or studies										
What is the efficacy of this intervention?	Effective / Ameliorative										
<p>∨ Magnesium Must be started within Hours</p> <p>Considered for acute anti-arrhythmic therapy only</p> <table border="0"> <tr> <td>How long after diagnosis does this intervention need to be started?</td> <td>Hours</td> </tr> <tr> <td>Age group in which this intervention may be started</td> <td>Neonate, Infant, Child</td> </tr> <tr> <td>Are there groups in which this intervention is contraindicated?</td> <td>No</td> </tr> <tr> <td>What is the level of evidence available for this intervention?</td> <td>Case report(s)</td> </tr> <tr> <td>What is the efficacy of this intervention?</td> <td>Effective / Ameliorative</td> </tr> </table> <p style="text-align: right;">COMMENT</p>		How long after diagnosis does this intervention need to be started?	Hours	Age group in which this intervention may be started	Neonate, Infant, Child	Are there groups in which this intervention is contraindicated?	No	What is the level of evidence available for this intervention?	Case report(s)	What is the efficacy of this intervention?	Effective / Ameliorative
How long after diagnosis does this intervention need to be started?	Hours										
Age group in which this intervention may be started	Neonate, Infant, Child										
Are there groups in which this intervention is contraindicated?	No										
What is the level of evidence available for this intervention?	Case report(s)										
What is the efficacy of this intervention?	Effective / Ameliorative										
<p>> Propranolol Must be started within Hours Contraindications</p> <p style="text-align: right;">COMMENT</p>											
<p>∨ Implantable cardioverter defibrillator Must be started within Days or Weeks, Years</p> <table border="0"> <tr> <td>How long after diagnosis does this intervention need to be started?</td> <td>Days or Weeks, Years</td> </tr> <tr> <td>Age group in which this intervention may be started</td> <td>Neonate, Infant, Child</td> </tr> <tr> <td>Are there groups in which this intervention is contraindicated?</td> <td>No</td> </tr> <tr> <td>What is the level of evidence available for this intervention?</td> <td>Cohort study or studies</td> </tr> <tr> <td>What is the efficacy of this intervention?</td> <td>Effective / Ameliorative</td> </tr> </table> <p style="text-align: right;">COMMENT</p>		How long after diagnosis does this intervention need to be started?	Days or Weeks, Years	Age group in which this intervention may be started	Neonate, Infant, Child	Are there groups in which this intervention is contraindicated?	No	What is the level of evidence available for this intervention?	Cohort study or studies	What is the efficacy of this intervention?	Effective / Ameliorative
How long after diagnosis does this intervention need to be started?	Days or Weeks, Years										
Age group in which this intervention may be started	Neonate, Infant, Child										
Are there groups in which this intervention is contraindicated?	No										
What is the level of evidence available for this intervention?	Cohort study or studies										
What is the efficacy of this intervention?	Effective / Ameliorative										

Figure S2: Screenshot of Acute Treatment Detail from Genome-To-Treatment (GTRx) for Timothy Syndrome-CACNA1C

GTRx™ Search for a condition... Index of Conditions Index of Genes About GTRx ALEXION Rady Children's Institute

FRUCTOSE INTOLERANCE, HEREDITARY

Alternate Name(s)
FRUCTOSE INTOLERANCE, HEREDITARY

Incidence
The incidence of hereditary fructose intolerance is estimated to be 1 in 20,000 to 30,000 individuals each year worldwide.

Inheritance
Autosomal recessive

Subspecialist Input Required
Nutritionist, Geneticist
Metabolic Specialist

Gene Information [SEQUENCE VIEWER](#)
ALDOB
Location: 9q31.1
Gene name: **aldolase, fructose-bisphosphate B** [NCBI GENE](#)
[GHR](#)

Recommended Acute Treatments and Interventions [COLLAPSE ALL](#)
Interventions that are appropriate for acute management of this diagnosis in an infant or child in an intensive care unit.

Fructose and sucrose free formula **Must be started within Hours**

How long after diagnosis does this intervention need to be started?	Hours
Age group in which this intervention may be started	Neonate, Infant, Child
Are there groups in which this intervention is contraindicated?	No
What is the level of evidence available for this intervention?	Authoritative published clinical practice guideline
What is the efficacy of this intervention?	Effective / Ameliorative

[COMMENT](#)

Clinical Summary
FRUCTOSE INTOLERANCE, HEREDITARY
Hereditary fructose intolerance is a condition that affects a person's ability to digest the sugar fructose. Fructose is a simple sugar found primarily in fruits. Affected individuals develop signs and symptoms of the disorder in infancy when fruits, juices, or other foods containing fructose are introduced into the diet. After ingesting fructose, individuals with hereditary fructose intolerance may experience nausea, bloating, abdominal pain, diarrhea, vomiting, and low blood sugar (hypoglycemia). Affected infants may fail to grow and gain weight at the expected rate (failure to thrive). Repeated ingestion of fructose-containing foods can lead to liver and kidney damage. The liver damage can result in a yellowing of the skin and whites of the eyes (jaundice), an enlarged liver (hepatomegaly), and chronic liver disease (cirrhosis). Continued exposure to fructose may result in seizures, coma, and ultimately death from liver and kidney failure. Due to the severity of symptoms experienced when fructose is ingested, most people with hereditary fructose intolerance develop a dislike for fruits, juices, and other foods containing fructose. Hereditary fructose intolerance should not be confused with a condition called fructose malabsorption. In people with fructose malabsorption, the cells of the intestine cannot absorb fructose normally, leading to bloating, diarrhea or constipation, flatulence, and stomach pain. Fructose malabsorption is thought to affect approximately 40 percent of individuals in the Western hemisphere; its cause is unknown.

List of References

Title	PMID	Year	Journal
Acute liver failure in neonates with undiagnosed hereditary fructose intolerance due to exposure from widely available infant formulas.	29510902	2018	Molecular genetics and metabolism

Print Excel Csv Copy Rows per page: 10 1-1 of 1

Human Phenotype Ontology (HPO) Terms Associated with FRUCTOSE INTOLERANCE, HEREDITARY [GARD HPO TERMS](#)

GTRx is provided for research use only and is not intended for clinical use. It has not been approved by the FDA. Users of this tool retain all responsibility for any medical decision-making including diagnosis, treatment and case management

Figure S3. Screenshot from GTRx for Hereditary Fructose Intolerance-ALDOB

REDCap
 Logged in as mowen1 | Log out
 My Projects

Project Home and Design

- Project Home
- Project Setup
- Designer
- Dictionary
- Codebook
- Project status: Development

Data Collection

- Record Status Dashboard - View data collection status of all records
- Add / Edit Records - Create new records or edit/view existing ones
- Record ID 1390-OMIM:601005** (R1: , R2: - CACNA1C, TIMOTHY SYNDROME, TS) [Select other record](#)

Data Collection Instruments:

- Gene
- Disease
- Select Interventions For Review**
- Intervention / Treatment
- List Of Interventions
- List Of Disease Treatment Publications
- Secondary Review
- RCIGM-generated Clinical Summary
- Disease Natural History
- Gene And Intervention Set
- Gene And Variant Set
- Pubmed Dataset
- Go Back Page

Applications

- Alerts & Notifications
- Calendar
- Data Exports, Reports, and Stats
- Data Import Tool
- Data Comparison Tool
- Logging
- Field Comment Log
- File Repository
- User Rights and DAGs
- External Modules

Reports

- 1) GTRx V2.0 eDSS Export
- 2) Concordance Abbreviated (10 plus 5)
- 3) Concordance 10 plus 5 abbreviated - resorted
- 4) Current Content List
- 5) Interventions and Publications
- 6) Interventions and types - Mallory Publication Data

External Modules

- Shazam Setup

Help & Information

- Help & FAQ

Rady Children's Institute for Genomic Medicine

GTRx (TM) PID 62

Actions: [Modify instrument](#) [Download PDF of instrument\(s\)](#) [VIDEO: Basic data entry](#)

Select Interventions For Review

Data Access Group: Complete_Ready_For_Export

Editing existing Record ID 1390-OMIM:601005 (R1: , R2: - CACNA1C, TIMOTHY SYNDROME, TS)

Record ID: 1390-OMIM:601005

GTRx™ Rady Children's Institute Genomic Medicine ALEXION

Please review the interventions, or groups of interventions provided below and identify which should be retained or deleted. Those selected will be present in subsequent pages for your review and comment.

Please select this button if there are no accepted treatments/interventions for this disease.

No treatment for this disease [reset](#)

Isoprenaline Retain Delete Add note about group

Why is this intervention inappropriate?

- Wrong treatment
- Inadequate evidence
- Not appropriate for intensive care setting
- Not specific for this disease
- Other

Please provide the "other" reason this intervention was deleted

Not a treatment for TS [Expand](#)

Fentanyl Retain Delete Add note about group

Why is this intervention inappropriate?

- Wrong treatment
- Inadequate evidence
- Not appropriate for intensive care setting
- Not specific for this disease
- Other

Propranolol Retain Delete Add note about group

Atenolol,Nadolol Retain Delete Add note about group

Midazolam Retain Delete Add note about group

Why is this intervention inappropriate?

- Wrong treatment
- Inadequate evidence
- Not appropriate for intensive care setting
- Not specific for this disease
- Other

Figure S4. Genome-To-Treatment (GTRx) RedCap review system for Timothy Syndrome-CACNA1C. Select Interventions For Review page.

Project status: Development

Data Collection

Record Status Dashboard
- View data collection status of all records

Add / Edit Records
- Create new records or edit/view existing ones

Record ID 1390-OMIM:601005
(R1:, R2: - CACNA1C, TIMOTHY SYNDROME, TS)
[Select other record](#)

Data Collection Instruments:

- Gene
- Disease
- Select Interventions For Review
- Intervention / Treatment**
- List Of Interventions
- List Of Disease Treatment Publications
- Secondary Review
- RCGM-generated Clinical Summary
- Disease Natural History
- Gene And Intervention Set
- Gene And Variant Set
- Pubmed Dataset
- Go Back Page

Applications

- Alerts & Notifications
- Calendar
- Data Exports, Reports, and Stats
- Data Import Tool
- Data Comparison Tool
- Logging
- Field Comment Log
- File Repository
- User Rights and DAGs
- External Modules

Reports [Search](#) [Organize](#) [Edit](#)

- 1) GTRx V2.0 eDSS Export
- 2) Concordance Abbreviated (10 plus 5)
- 3) Concordance 10 plus 5 abbreviated - resorted
- 4) Current Content List
- 5) Interventions and Publications
- 6) Interventions and types - Mallory Publication Data

External Modules

- Shazam Setup


Help & Information

- Help & FAQ
- Video Tutorials
- Suggest a New Feature

[Contact REDCap administrator](#)

Editing existing Record ID **1390-OMIM:601005** (R1:, R2: - CACNA1C, TIMOTHY SYNDROME, TS)

Record ID 1390-OMIM:601005



Condition Name: TIMOTHY SYNDROME; TS

OMIM #: 601005
Orphanet Disease ID: 65283

Gene Reviews: NBK1403
Medline: TIMOTHY SYNDROME; TS
Gard Disease ID: 9294

Gene associated with condition: CACNA1C

[List of Disease Treatment Publications](#)

Propranolol

Provide Comment reset

In what time frame does this intervention need to be started after diagnosis? reset

Hours
 Days or Weeks
 Years

In which age group should this intervention be used? reset

Neonate
 Infant
 Child

Are there any groups in which this intervention is contraindicated? reset

Yes
 No

For which subgroup is this intervention contraindicated? reset

Please classify the effectiveness of the intervention reset

Curative
 Effective / Ameliorative
 Still in Trials / Unproven
 Contraindicated

Highest category of evidence supporting efficacy of intervention. reset

1 Authoritative published clinical practice guideline
 2 Cohort study or studies
 3 Case report(s)

Comments (if any) regarding evidence supporting this intervention. reset

ADD NOTE

Beta blockers are the mainstay of treatment. Expert consensus is that nadolol is the best beta blocker for use in TS, with propranolol second best. Specific beta blocker use depends on age, acuity and route of administration.

Expand

Provide Comment

Figure S5. Genome-To-Treatment (GTRx) RedCap review system for Timothy Syndrome-CACNA1C. Intervention / Treatment page for Propranolol.

Project Home and Design

Project Home · Project Setup

Designer · Dictionary · Codebook

Project status: Development

Data Collection

Record Status Dashboard
- View data collection status of all records

Add / Edit Records
- Create new records or edit/view existing ones

Record ID: 1390-OMIM:601005
(R1: - CACNA1C, TIMOTHY SYNDROME, TS)
[Select other record](#)

Data Collection Instruments:

- Gene
- Disease
- Select Interventions For Review
- Intervention / Treatment
- List Of Interventions
- List Of Disease Treatment Publications**
- Secondary Review
- RCI/IGM-generated Clinical Summary
- Disease Natural History
- Gene And Intervention Set
- Gene And Variant Set
- Pubmed Dataset
- Go Back Page

Applications

- Alerts & Notifications
- Calendar
- Data Exports, Reports, and Stats
- Data Import Tool
- Data Comparison Tool
- Logging
- Field Comment Log
- File Repository
- User Rights and DAGs
- External Modules

Reports

Search Organize Edit

- 1) GTRx V2.0 eDSS Export
- 2) Concordance Abbreviated (10 plus 5)
- 3) Concordance 10 plus 5 abbreviated - resorted
- 4) Current Content List
- 5) Interventions and Publications
- 6) Interventions and types - Mallory Publication Data

External Modules

- Shazam Setup

Help & Information

- Help & FAQ
- Video Tutorials
- Suggest a New Feature


[Contact REDCap administrator](#)

List Of Disease Treatment Publications

Data Access Group: Complete_Ready_For_Export

Editing existing Record ID 1390-OMIM:601005 (R1: - CACNA1C, TIMOTHY SYNDROME, TS)

Record ID: 1390-OMIM:601005



Publication Type: Journal Name	Title (link to abstract)	PMID (link to full text)	Year of Publication	Notes on Content
Article: Experimental biology and medicine (Maywood, N.J.)	Dysfunctional Cav1.2 channel in Timothy syndrome, from cell to bedside.	31324123	2019	Ranolazine Low-dose mexiletine Mexiletine Verapamil Nifedipine Roscovitine Beta-blockers
<input type="radio"/> Leave Note	<small>reset</small>			
Article: The Journal of physiology	Impaired chromaffin cell excitability and exocytosis in autistic Timothy syndrome TS2-neo mouse rescued by L-type calcium channel blockers.	30629744	2019	Verapamil Nifedipine
<input type="radio"/> Leave Note	<small>reset</small>			
Publication: JACC. Clinical electrophysiology	Clinical Outcomes and Modes of Death in Timothy Syndrome: A Multicenter International Study of a Rare Disorder.	30067485	2018	Beta-blockers Atenolol Low-dose mexiletine Mexiletine Beta-blockers Beta-blockers Nadolol Left cervical sympathetic denervation Implantable cardioverter defibrillator
<input type="radio"/> Leave Note	<small>reset</small>			
Publication: Europace : European pacing, arrhythmias, and cardiac electrophysiology : journal of the working groups on cardiac pacing, arrhythmias, and cardiac cellular electrophysiology of the European Society of Cardiology	A multicentre study of patients with Timothy syndrome.	28371864	2018	Beta-blockers Atenolol Low-dose mexiletine Mexiletine Isoproterenol Beta-blockers Nadolol Implantable cardioverter defibrillator Permanent pacemaker

Figure S6. Genome-To-Treatment (GTRx) RedCap review system for Timothy Syndrome-CACNA1C. List Of Disease Treatment Publications page.

Logged in as **howell** | Logout

My Projects

Project Home and Design

- Project Home
- Project Setup
- Designer
- Dictionary
- Codebook
- Project status: **Development**

Data Collection

- Record Status Dashboard
 - View data collection status of all records
- Add / Edit Records
 - Create new records or edit/view existing ones

Record ID **1390-OMIM:601005**
(R1: -, R2: - CACNA1C, TIMOTHY SYNDROME; TS) [Select other record](#)

Data Collection Instruments:

- Gene
- Disease
- Select Interventions For Review
- Intervention / Treatment
- List Of Interventions
- List Of Disease Treatment Publications
- Secondary Review**
- RCIGM-generated Clinical Summary
- Disease Natural History
- Gene And Intervention Set
- Gene And Variant Set
- Pubmed Dataset
- Go Back Page

Applications

- Alerts & Notifications
- Calendar
- Data Exports, Reports, and Stats
- Data Import Tool
- Data Comparison Tool
- Logging
- Field Comment Log
- File Repository
- User Rights and DAGs
- External Modules

Reports [Search](#) [Organize](#) [Edit](#)

- GTRx V2.0 eDSS Export
- Concordance Abbreviated (10 plus 5)
- Concordance 10 plus 5 abbreviated - resorted
- Current Content List
- Interventions and Publications
- Interventions and types - Mallory Publication Data

External Modules

- Shazam Setup

Help & Information

- Help & FAQ
- Video Tutorials
- Suggest a New Feature

Actions: [Modify instrument](#) [Download PDF of instrument\(s\)](#) [VIDEO: Basic data entry](#)

Secondary Review

Data Access Group: **Complete_Ready_For_Export** [?](#)

Editing existing Record ID **1390-OMIM:601005** (R1: -, R2: - CACNA1C, TIMOTHY SYNDROME; TS)

Record ID 1390-OMIM:601005

Secondary Review of:
CACNA1C: TIMOTHY SYNDROME; TS

Condition Name: **TIMOTHY SYNDROME; TS**

OMIM #: **601005**
Orphanet Disease ID: **65283**

Gene Reviews: **NBK1403**
Medline: **TIMOTHY SYNDROME; TS**
Gard Disease ID: **9294**

Gene associated with condition: **CACNA1C**

List of Disease Treatment Publications

Emergency Notice: **WARNING: HIGH RISK OF HYPOGLYCEMIA DURING GENERAL ANESTHESIA.** Agree Disagree Leave Note

Sub-Specialist consult? **Yes** Agree Disagree Leave Note

Sub-Speciality identified: **Cardiology, Anesthesiology, Other Cardiology - Electrophysiology** Agree Disagree Leave Note

Treatment sub-populations identified? **No** Agree Disagree Leave Note

Isoprenaline: Delete

Reasons for deletion: **Other**
other comments on deletion: **Not a treatment for TS** Agree Disagree Leave Note

Notes for intervention: _____

Fentanyl: Delete

Reasons for deletion: **Wrong treatment**
other comments on deletion: _____ Agree Disagree Leave Note

Notes for intervention: _____

Propranolol: Retain

Reasons for deletion: _____
other comments on deletion: _____ Agree Disagree Leave Note

Notes for intervention: _____

Propranolol: Retain

Figure S7. Genome-To-Treatment (GTRx) RedCap review system for Timothy Syndrome-CACNA1C. Secondary Review page.

Supplementary Methods

GTRx General Principles for Intervention Review and Adjudication

1. Our scope is focused on providing **information for intensivists in an acute care setting** facing a new diagnosis of a rare genetic condition. Interventions that fall outside of this scope will not appear in the interventions list on the GTRx tool.
2. Our intent is **to include all interventions for which published evidence of efficacy or ameliorative effect in the specific disease being considered** is available.
 - a. Interventions that are not the first line, but for which evidence does exist, **will be** included.
3. Our scope includes treatments that are **used for condition-specific supportive care**, but not for general supportive care as would be routinely performed in an ICU setting.
 - a. Any intervention in which this distinction is unclear will be discussed and a consensus reached by the expert panel before inclusion.
4. Interventions that fall outside of the scope set out in 1 will be collected in a separate database, which will be periodically re-reviewed as new evidence becomes available. At such time when sufficient evidence accumulates to support the inclusion of these interventions, they will be added to the GTRx interface. Evidence will be re-reviewed on an ongoing basis each year.