EJP RD

European Joint Programme on Rare Diseases

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Del 13.1

Collection of (at least) 20 curated pathways in a (sub)portal on WikiPathways

Organisation name of lead beneficiary for this deliverable:
Partner 36 – UM

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Dissemination level: public

1. Summary

Creation of a rare disease portal on WikiPathways, a database for molecular pathways. The portal contains by now 90 rare disease pathways, which is 450% more than originally promised for month 36. Due to the combined effort of the UM team and other pathway curators and creators this delivery could be finished with more content than originally planned. We will continue to include and upgrade pathways according to the needs of existing and upcoming collaborations within EJP RD.

Project partners involved in Task 13.1.1" *Pathways created and expert curated. Build a knowledge base of relevant rare diseases biological pathways for the existing pathway portal available on WikiPathways*": **UM,** LUMC, ACU/ACURARE

Pathway authors: see Appendix

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2. The rare diseases portal on WikiPathways

The first task was to create a separate portal for rare diseases on WikiPathways. WikiPathways is an open, community curated database for biological pathways [Martens et al. 2021]. It covers more than 11500 unique human genes and their interactions. Among the genes involved in mendelian diseases, 66% of registered disease genes from OMIM are in WikiPathways. In June 2019 there were 2803 pathways available on WikiPathways for data analysis of which 1091 were for human.

The rare disease portal was installed as one of the several subportals of WikiPathways which hold collections of pathways for special interests, e.g. AOP (adverse outcome pathways), WormBase (*C. elegans* pathways), or lipids. The rare disease portal can be found under http://raredisease.wikipathways.org.

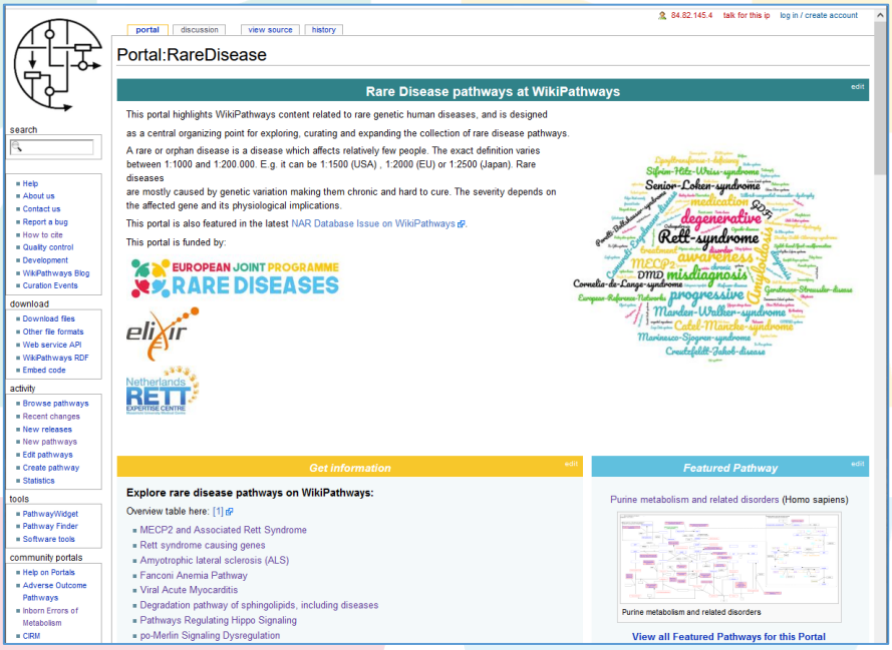

Figure 1. Rare disease portal on WikiPathways http://raredisease.wikipathways.org

3. The 90 rare disease pathways on WikiPathways

The second task was to raise the number of rare disease pathways to at least 20. Molecular pathways on WikiPathways are usually constructed by domain experts with training and/or guidance in using PathVisio as a pathway drawing software and support from WikiPathways curators. Several curators are also domain experts in different fields.

A molecular pathway consists basically of nodes and edges - genes, proteins, metabolites and other biological entities and their interactions. The software used for drawing and curating pathways is PathVisio [Kutmon et al. 2015]. Nodes are annotated with unique identifiers which can be derived from different databases or respectively identifier systems (e.g., metabolites, genes, proteins, or probe identifiers). The BridgeDb function in the background allows cross-referencing and identifier mapping [van Iersel et al. 2010]. A basic interaction is shown in Figure 2. The interactions between data nodes are annotated with MIM interactions, allowing to analyse pathways for directionality and giving the interactions a machine-readable

meaning, which can be used for specific analyses [Luna et al. 2011]. Commonly used MIM interactions are e.g., conversion, binding, inhibition, or stimulation.

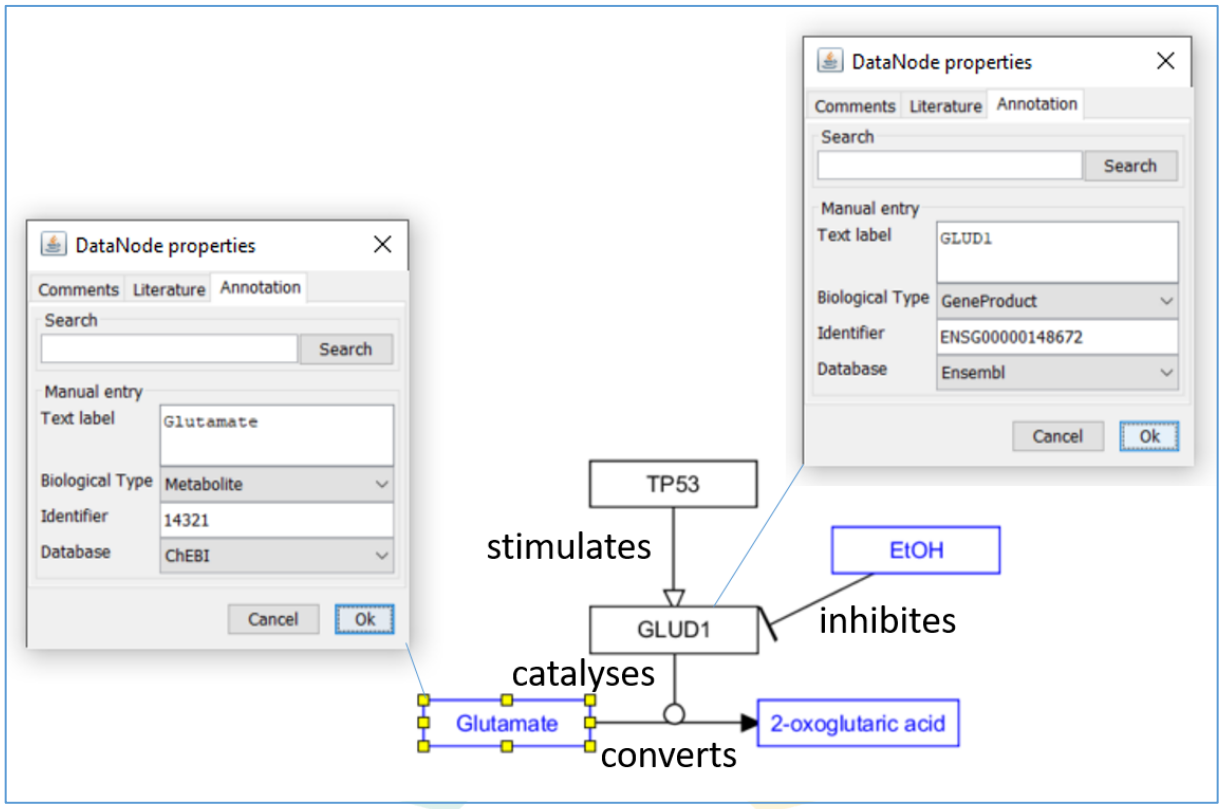

Figure 2. Example pathway. GLUD1 catalyses the conversion of glutamate to 2-oxoglutaric acid. GLUD1 expression is stimulated by TP53 and the enzyme is inhibited by ethanol. Glutamate annotation is linked to its ChEBI chemical compound identifier, GLUD1 to its E ENSEMBL identifier. Other annotations allow literature references and free text comments.

Further functions are formation of groups or complexes and the possibility to add non-annotated labels and graphical elements for better visualization. The pathways on WikiPathways can be annotated with information about the pathway type (from the Pathway ontology), disease (from the Disease ontology) and cell or tissue type in which this pathway was observed (from the Cell type ontology). Additionally, a history of edits including version tracking is added.

An example of a full molecular pathway can be found in Figure 3 on the example of Amyotrophic lateral sclerosis (ALS) pathway, a rare neurological disorder.

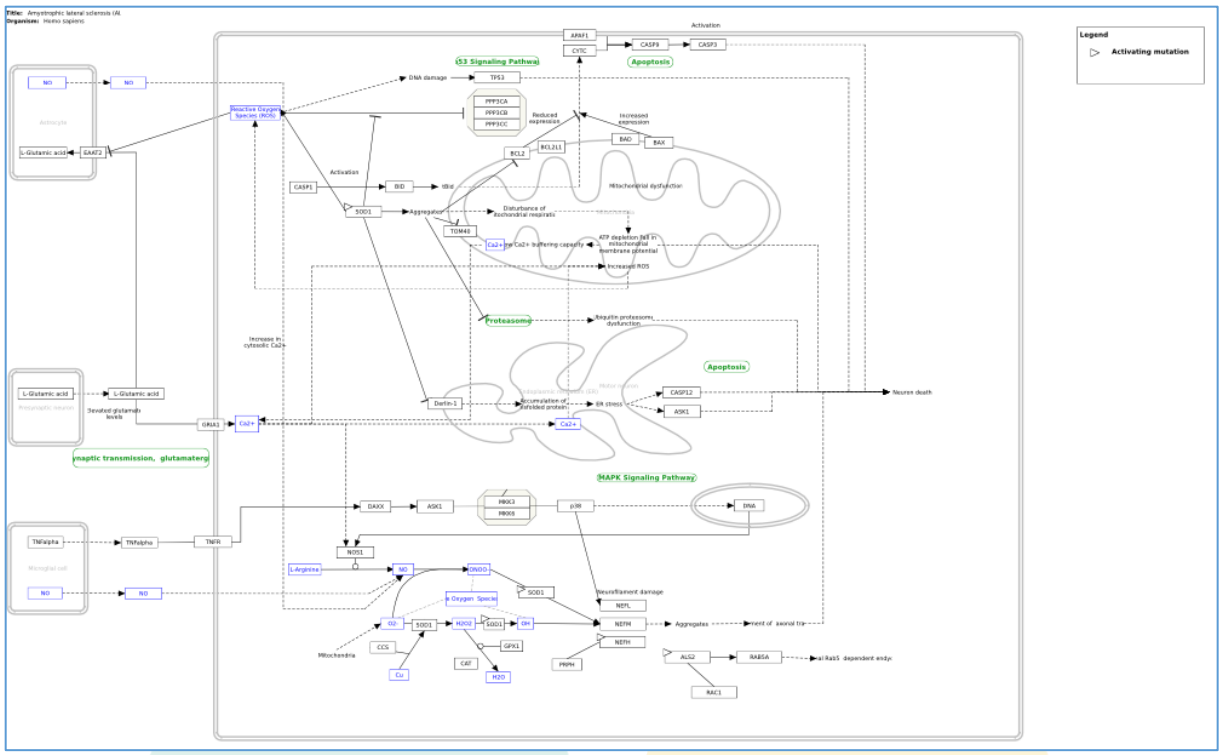

Figure 3. Pathway WP2447, about the molecular interactions leading to ALS

The portal holds at the moment (25.11.2021) 90 pathways for rare diseases. As some non-rare diseases like Alzheimer's and Parkinson's disease can be caused by rare genetic mutations (familial/hereditary disease) we included these pathways as well. A full list of the pathways and the responsible authors and curators can be found in the appendix 1.

An actual list of rare disease pathways (marked by the "rare disease community tag") can be found with this (non-persistent) link, alternatively directly on the rare disease portal:
https://www.wikipathways.org/index.php?title=Special:CurationTags&showPathwaysFor=Curation%3ARareDiseases

4. Additional work

4.1. Implementation of pathways and genes of interest due to requests from ERNs

From the first ERN survey conducted in 2019 we got the following responses when asking for genes, diseases, or pathways of interest.

Question A5. *Do you have any data on diseases/risk factors/drugs/metabolic/signaling pathways that could be added into an existing pathway or structured into a new one?*
Answers: ABCC8/KCNJ11; GK; GLUD1; HADH ATP7B and early "non-Wilson" liver disease, bone fragility, Candidate genes for POI, MEN or Congenital Hypothyroidism or Kallmann or Familial thyroid cancer, Cardiac genes, collection of blood samples (DNA) CSF biomarkers, Cytochrome polymorphisms (CYP2C19 and CYP2C9) in a selected number of Patients. Study design for other gene polymorphism Dyslipidemias ENG, ACVRL1 SMAD4, Gene panel involved in Thrombosis and haemostasis, genes involved in rhabdomyolysis, genes regulating red blood cell production and removal, genes related to collagenopathies, HBB gene, Hyperinsulinism, IL-1-related pathways in HS involved in Primary Immunodeficiencies, iron-related genes, more details on request directly to the group leader, oxidative stress, paediatric cholestasis, those involved in uro-rectal malformations, Variants from NGS panels, xeroderma pigmentosum

We have by now created pathways for the following diseases: Kallmann Familial thyroid cancer, Dyslipidemias, POI, MEN, and xeroderma pigmentosum. The following will be created in 2022: "non-Wilson" liver disease, Congenital Hypothyroidism, Hyperinsulinism, and paediatric cholestasis.

We checked for the individually mentioned genes, they were all findable in WikiPathways. For several diseases, groups of diseases (e.g. genes involved in …) we investigated the coverage (quite high) and have already or will include them in WikiPathways. See appendix 2 for full lists of genes related to certain diseases or processes.

4.2. Creation and curation of pathways for the Case studies together with clinical and biomedical experts.

Congenital anomalies of kidney and urinary tract (CAKUT) case study: Several pathways are available covering different aspects of the disease. In 2021 several workshops (First: 04.02.2021, follow up: 25.08.2021) have been conducted together with a group of about 15 biomedical and clinical experts. These experts were recruited via the ERN connections of Franz Schäfer. Together with pathway curation experts the pathways were shaped together, capturing the molecular interactions, time and spatial distribution of the molecular markers.

Inclusion Body Myositis (IBM) case study: Two pathways for IBM are now available. In November 30th 2021 a workshop with the case study data owners from Helsinki University was conducted to curate the first pathway drafts [link to document].

Idiopathic, non-cirrhotic portal vein hypertension (INCPH) case study: The data analysis has just started, the first pathway drafts are expected in the first half of 2022.

4.3. Education and training efforts

In November 2019 (26. - 29.11.) we organized a more tutorial workshop together with WP12 (FAIRification) in which we invited members from amongst other ERNs to learn how to create and curate pathways on WikiPathways [link to workshop].

We collaborated with the InterREG project Helis Academy for data analysis and data stewardship [link to Helis Academy] and contributed to several courses organised by Helis Academy.

Tutorial material was made available on the departments training pages, available on: https://pathvisio.org/tutorials and on TeSS [link to workshop material with Helis Academy].

Additionally, it should be noted that about 35 students from Maastricht University (mostly biomedical sciences, but also systems biology and Maastricht science program students) were trained on pathways for rare diseases during internships and project works.

5. Appendix

5.1. List of the 90 rare disease pathways, their authors and curators

To date, 71 different authors and curators contributed to the rare disease pathways. About half of them were students in training.

Pathway	Pathway ID and link	Authors and curators
Alzheimer's disease and miRNA effects	WP2059	Nathan Salomonis, Kristina Hanspers, Egon Willighagen, Friederike Ehrhart, Lovnish Thakur, Alexander Pico, Thomas Kelder, Eric Weitz, Jonathan Mélius, Susan Coort
Parkinson's disease pathway	WP2371	Alexander Pico, Kristina Hanspers, Egon Willighagen, Friederike Ehrhart, Eric Weitz, Martina Kutmon
Amyotrophic lateral sclerosis (ALS)	WP2447	Anders Riutta, Kristina Hanspers, Egon Willighagen, Alexander Pico, Finterly Hu, Martina Kutmon, Tyler Peryea, Denise Slenter, Friederike Ehrhart, Susan Coort
Fanconi Anemia Pathway	WP3569	Reactome Team, Martina Kutmon, Friederike Ehrhart
MECP2 and associated Rett syndrome	WP3584	Friederike Ehrhart, Kristina Hanspers, Egon Willighagen, Alexander Pico, Eric Weitz, Lauren J. Dupuis, Martina Kutmon, Ryan Miller
ERK pathway in Huntington's disease	WP3853	AAR&Co, Kristina Hanspers, Martina Kutmon, Andika Tan, Eric Weitz, Nirupama Benis
Prion disease pathway	WP3995	Lot van de Wouw, Friederike Ehrhart, Kristina Hanspers, Egon Willighagen, Finterly Hu, Martina Kutmon
Prader-Willi and Angelman syndrome	WP3998	Kelly Janssen, Friederike Ehrhart, Egon Willighagen, Kristina Hanspers, Alexander Pico, Anders Riutta, Denise Slenter, Eric Weitz, Finterly Hu, Martina Kutmon, Susan Coort
Degradation pathway of sphingolipids, including diseases	WP4153	Denise Slenter, Ado, Egon Willighagen, Kristina Hanspers, Andra Waagmeester, Finterly Hu, Friederike Ehrhart, Irene Hemel

Pathway	Pathway ID and link	Authors and curators
Biosynthesis and regeneration of tetrahydrobiopterin and catabolism of phenylalanine	WP4156	Denise Slenter, Egon Willighagen, Irene Hemel, Friederike Ehrhart, Daniela Digles, Finterly Hu, Josien Landman
GABA metabolism (aka GHB)	WP4157	Denise Slenter, Yasmin Omar, Egon Willighagen, Finterly Hu, Friederike Ehrhart
Neurotransmitter disorders	WP4220	AnneFriesacher, Denise Slenter, Egon Willighagen, Kristina Hanspers, Martina Kutmon, Eric Weitz, Finterly Hu, Irene Hemel
Purine metabolism and related disorders	WP4224	Roel Hacking, Denise Slenter, Josien Landman, Irene Hemel, Egon Willighagen, Kristina Hanspers, Daniela Digles, Finterly Hu, Friederike Ehrhart, Martina Kutmon
Pyrimidine metabolism and related diseases	WP4225	Roel Hacking, Denise Slenter, Irene Hemel, Egon Willighagen, Friederike Ehrhart, Finterly Hu, Martina Kutmon
Vitamin B6-dependent and responsive disorders	WP4228	Lisa Martina Held, Denise Slenter, Egon Willighagen, Susan Coort, Finterly Hu, Friederike Ehrhart, Irene Hemel, Kristina Hanspers, Martina Kutmon, Marvin Martens
Krebs cycle disorders	WP4236	Richard Delava, Denise Slenter, Egon Willighagen, Eric Weitz, Finterly Hu, Friederike Ehrhart, Irene Hemel, Josien Landman
Disorders of folate metabolism and transport	WP4259	Jesse Vercoulen, Denise Slenter, Andra Waagmeester, Egon Willighagen, Eric Weitz, Finterly Hu, Friederike Ehrhart, Irene Hemel, Josien Landman, Kristina Hanspers
Vitamin B12 disorders	WP4271	Mzolisi Mtshaulana, Denise Slenter, Egon Willighagen, Finterly Hu, Eric Weitz, Friederike Ehrhart, Irene Hemel, Kristina Hanspers
MTHFR deficiency	WP4288	Jesse Vercoulen, Denise Slenter, Josien Landman, Egon Willighagen, Friederike Ehrhart, Irene Hemel, Kristina Hanspers
Methionine metabolism leading to sulfur amino acids and related disorders	WP4292	Hermann Ritter, Denise Slenter, Egon Willighagen, Finterly Hu, Friederike Ehrhart, Elisson Lopes, Eric Weitz, Irene Hemel, Kristina Hanspers

Pathway	Pathway ID and link	Authors and curators
Thiamine metabolic pathways	WP4297	Youssef Walid, Denise Slenter, Egon Willighagen, Finterly Hu, Friederike Ehrhart, Irene Hemel
Acute viral myocarditis	WP4298	Olivier Traets, Friederike Ehrhart, Egon Willighagen, Kristina Hanspers, Eric Weitz, Finterly Hu, Marvin Martens
Lamin A-processing pathway	WP4299	Lora Simons, Friederike Ehrhart, Denise Slenter, Egon Willighagen, Laurent Winckers
Rett syndrome causing genes	WP4312	Max van Son, Denise Slenter, Friederike Ehrhart, Finterly Hu
Effect of progerin on genes involved in Hutchinson-Gilford progeria syndrome	WP4320	Lora Simons, Friederike Ehrhart, Denise Slenter, Eric Weitz
Cysteine and methionine catabolism	WP4504	Denise Slenter, Irene Hemel, Egon Willighagen, Daniel Domingo-Fdez, Finterly Hu, Friederike Ehrhart
Tyrosine metabolism	WP4506	Lauren J. Dupuis, Denise Slenter, Agustin Gonzalez-Vicente, Friederike Ehrhart, Egon Willighagen, Eric Weitz, Finterly Hu, G. Keulen, Irene Hemel
Molybdenum cofactor (Moco) biosynthesis	WP4507	Denise Slenter, Josien Landman, Egon Willighagen, Finterly Hu, Irene Hemel
Gamma-glutamyl cycle for the biosynthesis and degradation of glutathione, including diseases	WP4518	Lobke Meels, Denise Slenter, Egon Willighagen, Eline Sanders, Eric Weitz, Finterly Hu, Friederike Ehrhart, Irene Hemel
Cerebral organic acidurias, including diseases	WP4519	Britt Pieters, Denise Slenter, Egon Willighagen, Eveline Schoenmaker, Eric Weitz, Finterly Hu, Friederike Ehrhart, Irene Hemel
Glycosylation and related congenital defects	WP4521	Eveline Schoenmaker, Denise Slenter, Egon Willighagen, Britt Pieters, Friederike Ehrhart, Finterly Hu, Irene Hemel, Lauren J. Dupuis
Metabolic pathway of LDL, HDL and TG, including diseases	WP4522	Ingebude, Denise Slenter, Egon Willighagen, Finterly Hu, Friederike Ehrhart, Irene Hemel, Lobke Meels, Martina Kutmon

Pathway	Pathway ID and link	Authors and curators
Classical pathway of steroidogenesis with glucocorticoid and mineralocorticoid metabolism	WP4523	Eline Sanders, Denise Slenter, Egon Willighagen, Friederike Ehrhart, Eric Weitz, Finterly Hu, Ingebude, Irene Hemel
Alternative pathway of foetal androgen synthesis	WP4524	Eline Sanders, Denise Slenter, Egon Willighagen, Eric Weitz, Finterly Hu, Friederike Ehrhart, Irene Hemel
Envelope proteins and their potential roles in EDMD physiopathology	WP4535	Laurent Winckers, Alexander Pico, Friederike Ehrhart, Marvin Martens
Hippo signaling regulation pathways	WP4540	Alexander Pico, Eric Weitz, Friederike Ehrhart
Hippo-Merlin signaling dysregulation	WP4541	Alexander Pico, Eric Weitz, Marvin Martens
Oxysterols derived from cholesterol	WP4545	Denise Slenter, Egon Willighagen, Friederike Ehrhart, Matthew Conroy
Fragile X syndrome	WP4549	Megi Kass, Friederike Ehrhart, Andra Waagmeester, Egon Willighagen, Elisson Lopes, Eric Weitz, Finterly Hu, Martina Kutmon
Neurodegeneration with brain iron accumulation (NBIA) subtypes pathway	WP4577	Gwen Keulen, Denise Slenter, Friederike Ehrhart, Egon Willighagen, Kristina Hanspers, Martina Kutmon, Marvin Martens
Urea cycle and associated pathways	WP4595	Irene Hemel, Denise Slenter, Egon Willighagen, Friederike Ehrhart
Joubert syndrome	WP4656	Anna de Brouwer, Friederike Ehrhart, Egon Willighagen, Eric Weitz
22q11.2 copy number variation syndrome	WP4657	Friederike Ehrhart, Victor Avramov, Egon Willighagen, Lauren J. Dupuis, Magda M. Latorre
Male infertility	WP4673	Friederike Ehrhart, Egon Willighagen, Eric Weitz
Leucine, isoleucine and valine metabolism	WP4686	Amy Kutmon, Denise Slenter, Eric Weitz, Finterly Hu, Lauren J. Dupuis

Pathway	Pathway ID and link	Authors and curators
Serine metabolism	WP4688	Amy Kutmon, Denise Slenter, Finterly Hu, Friederike Ehrhart, Egon Willighagen, Eric Weitz, Kristina Hanspers, Yasmin Omar
Thyroid hormones production and peripheral downstream signaling effects	WP4746	Rik Lahaije, Friederike Ehrhart, Egon Willighagen, Eric Weitz, Lauren J. Dupuis, Marvin Martens
Purine metabolism	WP4792	Denise Slenter, Martina Kutmon, Finterly Hu, Lauren J. Dupuis
Ciliopathies	WP4803	Ritchie Lee, Alexander Pico, Kristina Hanspers
Cholesterol biosynthesis with skeletal dysplasia	WP4804	Ritchie Lee, Egon Willighagen, Kristina Hanspers, Denise Slenter, Eric Weitz, Friederike Ehrhart
Somatic sex determination	WP4814	JenG, Friederike Ehrhart, Eric Weitz
Genes controlling nephrogenesis	WP4823	Iulia Ioncu, Friederike Ehrhart, Finterly Hu, #
GDNF/RET signaling axis	WP4830	Friederike Ehrhart, Eric Weitz, #
Peroxiredoxin 2 induced ovarian failure	WP4835	Bas Lahaije, Friederike Ehrhart, Egon Willighagen, Laurent Winckers
Mammalian disorder of sexual development	WP4842	Anouk Wolters, Friederike Ehrhart, Egon Willighagen, Finterly Hu
Influence of laminopathies on Wnt signaling	WP4844	Zoe Barois, Egon Willighagen, Friederike Ehrhart, Eric Weitz, Finterly Hu, Lauren J. Dupuis
Kisspeptin/kisspeptin receptor system in the ovary	WP4871	Margit Janssen, Friederike Ehrhart, Egon Willighagen, Eric Weitz
Overlap between signal transduction pathways contributing to LMNA laminopathies	WP4879	Zoe Barois, Egon Willighagen, Friederike Ehrhart, Eric Weitz
1q21.1 copy number variation syndrome	WP4905	Friederike Ehrhart, Marvin Martens, Denise Slenter, Egon Willighagen

Pathway	Pathway ID and link	Authors and curators
3q29 copy number variation syndrome	WP4906	Friederike Ehrhart, Marvin Martens, Egon Willighagen
7q11.23 copy number variation syndrome	WP4932	Friederike Ehrhart, Egon Willighagen
15q11.2 copy number variation syndrome	WP4940	Friederike Ehrhart, Egon Willighagen
15q13.3 copy number variation syndrome	WP4942	Friederike Ehrhart, Egon Willighagen
Nitric oxide metabolism in cystic fibrosis	WP4947	Friederike Ehrhart, Eric Weitz
16p11.2 proximal deletion syndrome	WP4949	Friederike Ehrhart, Egon Willighagen, Kristina Hanspers
16p11.2 distal deletion syndrome	WP4950	Friederike Ehrhart, Egon Willighagen
Phosphoinositides metabolism	WP4971	Denise Slenter, Egon Willighagen
Proline and hydroxyproline pathways	WP5026	Denise Slenter, Egon Willighagen, Eric Weitz, Finterly Hu, Friederike Ehrhart
Glycine metabolism, including IMDs	WP5028	Denise Slenter, Eric Weitz, Andra Waagmeester, Egon Willighagen, Finterly Hu, Friederike Ehrhart
Amino acid transport defects (IEMs)	WP5029	Denise Slenter, Finterly Hu
Ethylmalonic encephalopathy	WP5030	Denise Slenter, Andra Waagmeester, Egon Willighagen, Eric Weitz, Finterly Hu, Friederike Ehrhart
Biotin metabolism, including IEMs	WP5031	Denise Slenter, Egon Willighagen, Eric Weitz, Finterly Hu
Riboflavin and CoQ disorders	WP5037	Denise Slenter, Egon Willighagen, Finterly Hu, Friederike Ehrhart
Development of ureteric collection system	WP5053	Friederike Ehrhart, #

Pathway	Pathway ID and link	Authors and curators
Kallmann syndrome	WP5074	Marijn Kerkhofs, Egon Willighagen, Eric Weitz, Alexander Pico, Friederike Ehrhart
Malignant pleural mesothelioma	WP5087	Franziska Kreidl, Marvin Martens, Egon Willighagen, Eric Weitz, Finterly Hu, Lauren J. Dupuis
Congenital generalized lipodystrophy (CGL)	WP5101	Ulas Babayigit, Eric Weitz, Friederike Ehrhart, Egon Willighagen
Familial partial lipodystrophy (FPLD)	WP5102	Ulas Babayigit, Eric Weitz, Egon Willighagen
Progeria-associated lipodystrophy	WP5103	Ulas Babayigit, Friederike Ehrhart, Eric Weitz
Acquired partial lipodystrophy / Barraquer-Simons syndrome	WP5104	Ulas Babayigit, Eric Weitz, Friederike Ehrhart
Meta pathway lipodystrophy, dyslipidaemia, and hyperlipidaemia	WP5105	Ulas Babayigit, Friederike Ehrhart
Familial hyperlipidaemia type 1	WP5108	Ulas Babayigit, Friederike Ehrhart
Familial hyperlipidaemia type 2	WP5109	Ulas Babayigit, Friederike Ehrhart
Familial hyperlipidaemia type 3	WP5110	Ulas Babayigit, Friederike Ehrhart
Familial hyperlipidaemia type 4	WP5111	Ulas Babayigit, Egon Willighagen
Familial hyperlipidaemia type 5	WP5112	Ulas Babayigit
Nucleotide excision repair in xeroderma pigmentosum	WP5114	Natalie Hinkova, Friederike Ehrhart
Inclusion body myositis	WP5120	Friederike Ehrhart, Eric Weitz, *
Alzheimer's disease	WP5124	Kristina Hanspers

Pathway	Pathway ID and link	Authors and curators
Inclusion body myositis	WP5142	Theodoros Zarotiadis, Friederike Ehrhart, Eric Weitz, *

Participants of the CAKUT pathways curation workshops 04.02.2021 and 25.08.2021: Friederike Ehrhart, Franz Schaefer, Chris Evelo, Esra Kesdiren, Ruthild Weber, Anne Christians, Jörn Helge Martens, Marvin Martens, Norman Rosenblum, Lauren Dupuis, Lina Karen Werfel, Joost-Peter Schanstra, Andreas Schedl, Jacqueline Ho, Benjamin, Jumamurat Bayjanov, Adrian Woolf, Matias Simons,

*Participants of the IBM pathway curation workshop 30.11.2021: Mridul Johari (Helsinki University, Jumamurat Bayjanov (RUMC), Friederike Ehrhart, Theodoros Zarotiadis, Lars Eijssen (UM)

5.2. The diseases, genes and processes mentioned in the ERN survey and their follow up

5.2.1. Diseases of interest mentioned in the ERN survey

Diseases (mentioned in the ERN survey)	Pathways
"non-Wilson" liver disease	To be covered first half of 2022 together with INCPH case study
Congenital Hypothyroidism / Kallmann Familial thyroid cancer	WP4928
Dyslipidemias	WP5105 and the 10 more pathways linked there
Hyperinsulinism	To be covered second half of 2022
Paediatric cholestasis	To be covered first half of 2022
Xeroderma pigmentosum	WP5114
Congenital Anomalies of Kidney and Urinary Tract (CAKUT)	WP5053; WP4823; WP5052; WP4830

5.2.2. Genes of interest mentioned in the ERN survey

Genes (mentioned in the ERN survey)	Pathways
ABCC8	WP1831, WP2669
HADH	WP2740, WP4031, WP3925
GK	4 pathways
KCNJ11	4 pathways
ATP7B	WP3286, WP4098
ENG	WP3668, WP560
ACVRL1	WP2760
SMAD4	37 pathways
HBB	8 pathways
"Genes involved in collagenopathies"	A list of genes involved in collagenopathies was collected from Jobling et al. (2014). https://doi.org/10.1007/s11926-013-0394-3: COL1A1, COL1A2, COL2A1, COL3A1, COL4A1, COL4A2, COL4A3, COL4A4, COL4A5, COL4A6, COL5A1, COL6A1, COL7A1, COL9A1, COL9A2, COL9A3, COL10A1, COL11A1, COL11A2, COL17A1, COL18A1. Each of those genes can be found in WikiPathways, in up to 31 different pathways.
"Genes involved in Premature Ovarian Insufficiency (POI)"	A list of genes involved in POI was collected from Jiao et al. (2017) https://doi.org/10.1210/jc.2016-3960: AMH, CDH1, CDKN1B, CYP11A1, CYP19A1, DMC1, EXO1, FIGLA, FMR1, FSHR, GDF9, INHA, MCM8, MSH5, NR5A1, PGRMC1, PRIM1, PTEN, SKP2, TCF3, WT1 These genes can be found in WikiPathways, e.g. in the pathways for disorders of sex development. CSB-PGBD3, HELQ, NANOS3, NOBOX, SOHLH1, SOHLH2 For these genes new pathways or additions to existing pathways are planned in 2022/23

Genes (mentioned in the ERN survey)	**Pathways**
"Genes involved in male infertility"	A list of genes involved in POI was collected from Krausz et al. (2015) https://doi.org/10.1530/REP-15-0261: ABCB1, ABLIM1, AHR, AHRR, APOB, ARNTL, ATM, BCL2, BHMT, BRCA2, CAT, CDC42BPA, CHD2, CLOCK, CRISP2, CYP1A1, CYP17A1, CYP26B1, EPSTI1, ERCC1, ERCC2, ETV5, FAS, FASLG, FOLH1, GNAO1, GPX1, HLA-DRA, JMJDIA, KLK2, LIG4, LOC203413, LRWD1, UBD, MAS1L, MCT2 (SLC16A7), MDM2, MLH1, MLH3, MSH4, MSH5, MTHFD1, MTHFR, MTR, MTRR, NFE2L2 (NRF2), NOS1, NOS2, NOS3, NQO1, OR2W3, PACRG, PARP1, PCFT1, PEMT, PEX10, PMS2, POLG, PON1, PON2, PSAT1, RAG1, RFC1, RGS9, SHMT1, SFRS1, SFRS2, SFRS3, SFRS4, SFRS5, SFRS6, SFRS7, SFRS9, SIRPA, SIRPG, SOD2, SOD3, SOX5, TAS2R38, TCblR, TCN2, TMEM132E, TNF, TP53, UBR2, USP26, USP8, XPC, XRCC2, XRCC3, XRCC4, XRCC5, BRDT, DAZL, EPPIN, H2BFWT, HORMAD1, HORMAD2, MOV10L1, NANOS1, PIWIL1, PIWIL2, PIWIL3, PIWIL4, PRDM9, PRM1, PRM2, PRMT6, REC8, SEPT12, SPATA17, SPO11, STRA8, TEX15, TSSK4, TSSK6, UBE2B, YBX2, AR, ESR1, ESR2, INSR, MSMB, SRD5A2 All genes are covered in WikiPathways, e.g. in WP4673.
"Genes involved in rhabdomyolysis"	The following hereditary disorders of the muscle energy supply may cause recurrent and usually exertional rhabdomyolysis: • Glycolysis and glycogenolysis defects: McArdle's disease, phosphofructokinase deficiency, glycogen storage diseases VIII, IX, X and XI • Lipid metabolism defects: carnitine palmitoyltransferase I and II deficiency, deficiency of subtypes of acyl CoA dehydrogenase (LCAD, SCAD, MCAD, VLCAD, 3-hydroxyacyl-coenzyme A dehydrogenase deficiency), thiolase deficiency • Mitochondrial myopathies: deficiency of succinate dehydrogenase, cytochrome c oxidase and coenzyme Q10 • Others: glucose-6-phosphate dehydrogenase deficiency, myoadenylate deaminase deficiency and muscular dystrophies The processes and genes mentioned here are covered within WikiPathways, e.g., in the pathways for inborn errors of metabolism.
"Genes involved in Iron metabolism"	Covered in WP4577
"Genes involved in Primary Immunodeficiencies"	To be covered in 2022
"Genes regulating red blood cell production and removal"	To be covered in 2022

Genes (mentioned in the ERN survey)	Pathways
"Gene panel involved in Thrombosis and haemostasis "	To be covered in 2022