Zebrafish models for congenital disorders of glycosylation (CDG): a systematic review

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Summary

- Glycosylation, or the addition of sugar chains, is very important to the function of many proteins. **~70% of proteins are glycosylated**. When this process is impaired, it can cause CDG
- **Animal models** are a powerful tool used by researchers to better understand CDGs. One of these models is the **zebrafish**, a small fish that shares many similarities with humans
- This study performed a **comprehensive search of the existing research** on zebrafish and CDG. 36 studies were identified and were summarized in this article to understand how useful zebrafish are for studying these disorders
- **The analysis revealed**:
    - Most existing research focused on **N-glycosylation (50% of studies)**
    - **Zebrafish genes are very similar to human genes (up to 92% identical)**, meaning what is learned in a zebrafish model often applies to people with CDG. This also makes zebrafish useful models to test gene editing techniques
    - **Zebrafish can show similar symptoms to humans** with CDG. Many of the physical and biological features seen in people with CDG can also be observed in zebrafish models
    - Researchers most often use a **specific technique** in these studies to **"turn off" genes** in zebrafish. This helps them understand what happens when specific genes don't work properly

Key Takeaway – Zebrafish are proving to be a powerful tool for CDG research. This study highlights how zebrafish can overcome the challenge of studying these complex conditions in humans and help provide key insights into how these disorders develop and present clinically, an essential step towards improving understanding and advancing effective treatments.

Why Zebrafish?

It might seem surprising that a small tropical fish could help scientists understand human genetics, but zebrafish are remarkably similar to humans at a biological level.

Feature	Benefit for CDG Research
Genetic Similarity	Approximately **76-82% of human genes** have a counterpart in zebrafish that are specifically linked to human diseases. Therefore, this organism is used extensively in research of genetic diseases. In addition, zebrafish genomes (which corresponds to the code used to make proteins) are **up to 90% similar** to the human genome, making them ideal for testing gene editing therapies
Transparent Embryos	Zebrafish embryos are clear, allowing scientists to watch organs like the heart, brain, and liver develop in real-time without invasive procedures.
Rapid Development	A zebrafish grows from a single cell to a swimming larva with most major organs in just **five days**, speeding up the pace of research.
Large Numbers	A single pair of fish can produce hundreds of offspring every week, providing a large "population" for testing potential new drugs.

👉 **What this means:** Findings in zebrafish are often **relevant to humans**, making them a powerful research tool for studying human diseases. Certain features regarding their development also can make **zebrafish research faster without the need for complex procedures** to make experimental observations compared to other more complex models like mice.

🔬 How Was This Research Carried Out?

This systematic review of scientific literature (covering studies up to late 2024) **identified 89 studies** which were refined to **34 key articles** that used zebrafish to study various types of CDG. These were curated from a range of sources, and used specific inclusion and exclusion criteria, to ensure **comprehensive and focused coverage of the most relevant work** from existing literature.

🧬 What types of glycosylation are being studied? *(see table below)*

- **N-glycosylation** → most studied (about 50% of all studies)
- **O-glycosylation** → 25% of studies
- **Proteins involved in multiple types of glycosylation** → 22% of studies
- **Other glycosylation types** → remaining portion, or 3%

N-glycosylation		O-glycosylation		Multiple glycosylation		Others	
PMM2	4	*B3GALT6*	1	*COG4*	3	*PIGK*	1
DHDDS	2	*B3GALNT2*	1	*GMPPB*	2		
FUT8	2	*B4GALT7*	1	*NANS*	1		
MAGT1	2	*DAG1*	1	*SLC35C1*	1		
MPI	2	*POFUT1*	1	*TRAPPC11*	1		
B4GALT1	1	*POMK*	1				
DPMS	1	*POMGNT1*	1				
MGAT5A	1	*POMT1*	1				
PRKCSH	1	*SLC26A2*	1				
SLC10A7	1						
TMEM165	1						

🧬 Which genes were the most studied?

The most frequently studied genes were **PMM2** (the most common CDG) and **COG4**. The next most studied genes included **DHDDS, FUT8, MAGT1, GMPPB**.

- **NOTE:** A full list of specific CDG zebrafish models that have been created and studied can be found in the original research article with descriptions for each on: what disease-relevant symptoms researchers saw, what treatments have been tested, and the treatment effect.

👉 **What this means:** Researchers are focusing most on the **most common and well-known CDG types**, but other types are starting to get attention too.

🌎 Where is this research happening?

Zebrafish research started in the early 2000s and increased significantly after **zebrafish genome sequencing** (around 2013) and over **400 researchers** have contributed to papers related to zebrafish models for CDG. The most prolific author is **Dr. Hudson Freeze**, followed by **Drs. Kirsten Sadler, Mark Lehrman,** and **Richard Street**.

- **North America accounts for 66% of research,** with the United States being the largest contributor (60%) and Canada contributing 6%

- **17% originate from Asia**, primarily from China (11%) and Japan (6%)
- **Europe accounts for 17%**, distributed across the UK and Belgium (both 6%), and Italy and The Netherlands (both 3%)

👉 **What this means:** As research tools improved, and more CDGs were discovered, research in this area accelerated leading to more discoveries. Importantly, CDG research using zebrafish is a **global effort**, with strong collaboration between scientists and clinicians. When experts around the world work together it improves efficiency, can speed up discoveries, helps ensure studies are scientifically rigorous and clinically relevant by learning from more patients, and helps keep research patient-centered.

🧪 How scientists study CDG in zebrafish

- Common techniques to create models of CDG:
    - **Morpholinos (most used)** → temporarily "turns off" a targeted gene. A morpholino is designed to find the gene and mask it from the cell's protein-making machinery. This blocks it from being made for the short period of time that the morpholino exists
    - **CRISPR/Cas9** → permanently edits genes to create specific gene variants or to completely inactivate a targeted gene
    - Other methods include **chemical mutagenesis** (permanent but induces random changes, not targeted) and **human gene injections** via mRNA (temporary and targeted)

👉 **What this means:** Researchers can **recreate CDG in zebrafish** using many different techniques to see what happens when specific genes don't work properly to **better understand the disorder**, or to **test new therapies** or screen potential drugs in a relevant model of the CDG type.

🧠 What symptoms zebrafish show (and how they relate to CDG)

Zebrafish models show many features similar to people with CDG:

- **Growth and physical development:** seen in zebrafish as smaller body size, abnormally small eyes, and shortened fins
- **Facial and structural differences:** changes in skull and facial cartilage
- **Sensory issues:** vision problems (including missing light-sensing cells), hearing/balance issues
- **Movement and muscle function:** weak or abnormal muscle development, difficulty swimming or unusual movement
- **Brain and nerve development:** developmental abnormalities in important brain cells, such as shortened neural axons
- **Other findings:** short lifespan or early death in severe cases, liver changes, heart rate differences, pigmentation changes

💊 Efforts to 'rescue' these phenotypes have tested therapeutic strategies, such as:

- **Sugar Supplementation**: In some CDG types, simply adding a specific sugar (like mannose or galactose) to the water where the fish live has been shown to "rescue" or fix the developmental problems. This provides strong evidence for trying similar dietary therapies in humans
- **Drug Screening:** Because zebrafish are small and live in water, researchers can add different chemical compounds to their environment to see if any can reverse the effects of the genetic mutation. This High-Throughput Screening is a primary way new medicines are discovered

👉 **What this means:** Zebrafish can **mirror many real symptoms seen in CDG** helping researchers understand how the disease affects the body. But zebrafish are not just for understanding disease; they are also being **used to test possible treatments**.

Key Outcomes and Final Conclusions

This study was the first comprehensive review looking at how zebrafish are used to study CDG, which highlighted **many benefits of zebrafish** models due to their **strong match to human biology**. Genes involved in glycosylation are very similar between zebrafish and humans and CDG models have been shown to reflect real patient symptoms. This allows scientists to better understand why symptoms happen, connect specific genes to specific features, identify possible treatment targets, and efficiently test drug candidates due to their fast growth and development.

This study also identified several **challenges** that continue to **slow overall progress**:

- **CDGs are not always clearly or consistently named** in research – some studies look at the same genes or pathways but do not explicitly mention 'CDG' making this information harder to find and connect; discoveries may be essentially 'lost' because they are not recognized as CDG-related
- **CDGs are not all classified in the same way**, which can happen for a few reasons:
    - No consistent definition of what 'counts' as a CDG. For example, genes that directly contribute to glycosylation are typically characterized as a CDG but genes that support the process indirectly, like transporters, may not be in some sources
    - Genes or diseases that are poorly understood or not clearly categorized can lead to them being overlooked or separated from CDG research (Example: dystroglycanopathies)
    - Patients, and research groups, are scattered globally – though there have been efforts to standardize terminology across countries and research groups, the low prevalence and global dispersion of patients, and the tendency to form isolated clusters for professional collaboration, limit the effectiveness of these efforts in practice
- **Mismatch between research focus and disease diversity** – more research has focused on N-glycosylation, though in 2022 there were more identified O-glycosylation disorders. Some conditions may be understudied or underdiagnosed partly due to naming and classification issues. However, due to improved tools, knowledge of O-glycosylation has expanded in recent years

❤️ Bottom line for families

Zebrafish are a powerful tool for understanding CDG and developing future therapies. Because many of their genes – especially those involved in glycosylation – function similarly to human genes, they help bridge the gap between gene discovery and real-world disease. Scientists can study many zebrafish at once and observe how the disease develops in real time, providing insight into how specific gene changes lead to symptoms seen in people with CDG. They offer a fast, effective, and human-relevant way to study the disease and test potential treatments.

Despite ongoing challenges, the field is making steady progress. New technologies and growing knowledge are helping fill key gaps, global research efforts are expanding, and stronger collaboration and more consistent classification will be essential to accelerating future advances.