Clinical, Pathological and Molecular Spectrum of Patients with Glycogen Storage Diseases (GSDs)- First Report from Pakistan

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Objectives

Data on GSDs is scarce from Pakistan. We present the first study from Pakistan to report a large cohort of heterogeneous hepatic GSDs patients characterized on enzymatic and/or molecular level.

Materials and Methods

• A cross sectional medical chart review was conducted

• A total of 55 clinically suspected patients supplemented initial biochemical work up suggestive of GSDs, presenting at the biochemical genetics’ clinic from January 2008 – December 2020 were included in this study.

• The extracted genomic DNA was outsourced to Invitae laboratory, San Francisco, USA for the Multi-Gene GSD panel through NGS platform.

• The NGS platform used was Illumina technology that offers full-gene sequencing and deletion/duplication analysis, achieving >99% analytical sensitivity and specificity for single nucleotide variants (SNVs).

• Liver biopsy was performed for enzyme activity analysis for only two patients in first year of the study period when NGS based testing was not widely available and single gene sequencing was very expensive.
Results

Figure 1 Flowchart of patients included in the study (n=55)
Family ID | Patient No | Gender | Clinical Presentation | Biochemical Analysis
--- | --- | --- | --- | ---
1 | 1 | M | Hepatomegaly, Doll-like facies. Inc ALT, Fasting Hypoglycemia, Hypercholesterolemia, Hyperuricemia | Inc ALT, Fasting Hypoglycemia, Hypercholesterolemia, Hyperuricemia
1 | 2 | M | Hepatomegaly, Hypoglycemic seizures Inc ALT, Fasting Hypoglycemia, Hypercholesterolemia, Hyperuricemia | Inc ALT, Fasting Hypoglycemia, Hypercholesterolemia, Hyperuricemia
1 | 3 | F | Hepatomegaly, Hypoglycemic seizures Inc ALT, Fasting Hypoglycemia | Inc ALT, Fasting Hypoglycemia
1 | 4 | F | Vomiting and sudden breathing, recovered shortly, oral intake tolerable, allergy reaction to egg white. Inc ALT, Hyperlactatemia | Hyperlactatemia
1 | 5 | F | Recurrent diarrhea, episodic neutropenia, short stature, scalp and neck, hepatic masses, Proximal muscular weakness/ Gower’s sign. Hepatomegaly | Inc ALT, Hyperlactatemia, Hypercholesterolemia
1 | 6 | M | Hepatomegaly, Recurrent diarrhea, short stature and neutropenia Inc ALT, Hyperlactatemia, Hypercholesterolemia | Inc ALT, Hyperlactatemia, Hypercholesterolemia
1 | 7 | M | Hepatomegaly, Fluid blood and Malaise positive, short stature, delayed teeth on face, hands and abdomen, Proximal muscular weakness/ Gower’s sign | Inc ALT, Hyperlactatemia, Hypercholesterolemia, Hyperuricemia
1 | 8 | M | Short stature, delayed teeth on face, hands and abdomen, Hepatomegaly | Inc ALT, Hyperlactatemia, Hypercholesterolemia
1 | 9 | M | Hepatomegaly, Hypoglycemic seizures at birth, Doll like facies | Inc ALT, Hyperlactatemia, Hypercholesterolemia
1 | 10 | M | Hepatomegaly, Recurrent infections, cough and respiratory distress, doll like facies | Inc ALT, Hyperlactatemia, Hypercholesterolemia
1 | 11 | F | Hepatomegaly, Doll-like facies, VS deficiency, metabolic, increases activity level, short stature, Proximal muscular weakness/ Gower’s sign | Inc ALT, Fasting Hypoglycemia, Hypercholesterolemia
1 | 12 | M | Hepatomegaly, Seizures, body stiffness and on and off drowsiness | Inc ALT, Fasting Hypoglycemia, Hypercholesterolemia, Hyperuricemia
1 | 13 | F | Hepatomegaly, Doll-like facies, short stature, early morning seizures, and hypoglycemia in early morning | Inc ALT, Fasting Hypoglycemia, Hypercholesterolemia
1 | 14 | M | Hepatomegaly, Fetus to thrive, Wasting body habitus, Developmental delay | Inc ALT, Hyperuricemia, Hypercholesterolemia
1 | 15 | M | Hepatomegaly, Recurrent vomiting, and hypoglycemia, Moderate bilateral distortion, Hepatomegaly | Inc ALT, Fasting Hypoglycemia, Hypercholesterolemia
1 | 16 | M | Hepatomegaly, Recurrent jaundice, abdominal pain and vomiting, Proximal muscular weakness/ Gower’s sign | Inc ALT, Fasting Hypoglycemia
1 | 17 | M | Tongue, and persistent lethargy, hepatomegaly, Doll like faces | Inc ALT, Fasting Hypoglycemia
1 | 18 | M | Hepatomegaly, Delayed rib formation, achondroplasia posture on eggshell, Proximal muscular weakness/ Gower’s sign | Inc ALT, Hypercholesterolemia
1 | 19 | M | Hepatomegaly, tilted in trunk and head | Inc ALT, Fasting Hypoglycemia
1 | 20 | M | Seizures not associated with hyperglycemia, Melena and jaundice, distal and proximal ischads, Metabolic and Developmental delay | Inc ALT, Fasting Hypoglycemia, Hypercholesterolemia
1 | 21 | M | Bell’s facies, Hepatomegaly | Inc ALT, Fasting Hypoglycemia
1 | 22 | M | Bell’s facies, Hepatomegaly, Recurrent diarrhea, Proximal muscular weakness/ Gower’s sign | Inc ALT, Hypercholesterolemia
1 | 23 | M | Hepatomegaly, History of diarrhea and Retinoic acid fed | Inc ALT, Fasting Hypoglycemia
1 | 24 | M | Short stature, Hepatomegaly, Doll like faces | Inc ALT, Fasting Hypoglycemia, Hypercholesterolemia, Hyperuricemia
1 | 25 | M | Short stature, Hepatomegaly, Doll like Faces | Inc ALT, Hyperuricemia
1 | 26 | M | Hepatomegaly, Bell’s facies, Proximal muscular weakness/ Gower’s sign | Inc ALT, Fasting Hypoglycemia
1 | 27 | M | Recurrent episodes of hypoglycemia, Short stature, Hepatomegaly | Inc ALT, Fasting Hypoglycemia
1 | 28 | M | Hepatomegaly, Doll like faces, short stature, weak hands, rare and then mild | Inc ALT, Hyperlactatemia, Hypercholesterolemia
1 | 29 | M | Hepatomegaly, Seizures with tonic seizures, Doll like faces, Truncal Paralysis | Inc ALT, Fasting Hypoglycemia
1 | 30 | M | Short stature, Hepatomegaly, Bell’s facies | Inc ALT, Fasting Hypoglycemia, Hypercholesterolemia, Hyperuricemia
1 | 31 | M | Short stature, Hepatomegaly, Doll like faces | Inc ALT, Hyperuricemia
1 | 32 | M | Hepatomegaly, Bell’s facies | Inc ALT, Fasting Hypoglycemia
1 | 33 | F | Hepatomegaly, short stature | Inc ALT, Fasting Hypoglycemia
1 | 34 | M | Hepatomegaly, short stature, Doll like faces, 6,4-gene virgum | Inc ALT, Fasting Hypoglycemia
1 | 35 | M | Hepatomegaly, thickened delay | Inc ALT, Fasting Hypoglycemia
1 | 36 | M | Hepatomegaly, thickened delay | Inc ALT, Fasting Hypoglycemia

Clinical and Biochemical Spectrum of patients with type specified GSDs

- **INBORN ERRORS OF METABOLISM**
- **Proximal muscular weakness/ Gower’s sign**
- **Fasting Hypoglycemia**
- **Seizures not associated with hyperglycemia, Melena and jaundice**
- **Bell’s facies, Hepatomegaly, Proximal muscular weakness/ Gower’s sign**
- **Seizures**
- **Hypoglycemia, History of diarrhea and Retinoic acid fed**
- **Short stature, Hepatomegaly, Bell’s facies**
- **Recurrent episodes of hypoglycemia**
- **Hepatomegaly, Doll like faces, short stature**
- **Hepatomegaly, Seizures with tonic seizures, Doll like faces**
- **Short stature, Hepatomegaly, Bell’s facies**
- **Hepatomegaly, Bell’s facies**
- **Hepatomegaly, short stature**
- **Hepatomegaly, thickened delay**
- **Hepatomegaly, 6,4-gene virgum**
- **Hepatomegaly, thickened delay**
- **Bell’s facies, Hepatomegaly**
- **Hypoglycemia, History of diarrhea**
- **Hypoglycemia, History of diarrhea and Retinoic acid fed**
- **Short stature, Hepatomegaly, Bell’s facies, proximal muscular weakness Gower’s sign**
The five novel variants identified in *SLC37A4*, *AGL* and *PYGL*

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**Conclusion**

Fifty-five patients of GSDs in 26 families from a single care provider indicate a relatively high frequency of GSD in Pakistan, with multiple unrelated families harboring identical disease-causing variants, on molecular analysis, including two known pathogenic variants in *SLC37A4* and *PHKG2*, and a novel variant in *AGL*. We report a spectrum of GSD subtypes and sequence variants identified in 33 patients. Eighteen variants, that matched the established mode of inheritance, were identified in seven genes that are associated with distinct GSD subtypes. Lack of awareness of physicians in the country about the manifesting phenotype of GSDs and meager diagnostic facilities are two major underlying factors for missed diagnoses of GSDs, with subsequent adverse patient outcomes.