# Hereditary Hyperekplexia in Saudi Arabia

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## ABSTRACT


### BACKGROUND

Hereditary hyperekplexia, a genetic defect leading to dysfunction of glycinergic inhibitory neurotransmission, is characterized by the clinical core features of exaggerated startle responses to unexpected sensory stimuli, recurrent apneas, and stiffness. So far, pathogenic variants in 3 genes relating to the glycinergic neurotransmission system have been identified in hereditary hyperekplexia: *GLRA1*, *SLC6A5*, and *GLRB. GLRA1* and *GLRB* encode post-synaptic proteins and *SLC6A5* encodes a pre-synaptic protein. Hereditary hyperekplexia is a rare but potentially treatable neurogenetic disorder.

### Objectives

To provide a comprehensive epidemiologic information, prevalence figures, and clinical characteristics of a large cohort of hereditary hyperekplexia patients in Saudi Arabia .

### METHODS

We retrospectively reviewed Saudi patients with genetically confirmed hereditary hyperekplexia using a standard questionnaire that was sent to 9 major referral hospitals in Saudi Arabia.

### RESULTES

Results Demographic and molecular data Twenty-two Saudi patients (11 males, 11 females) with hereditary hyperekplexia were identified. Seventeen patients (77%) had first-degree consanguineous parents.. The following genes were identified through molecular studies: SLC6A5 (12 patients, 54.5%), GLRB (seven patients, 31.8%), and GLRA1 (3 patients, 13.7%). No patient with ATAD1-related hyperekplexia was identified. All patients were homozygous for their respective variants. Twelve of these variants were novel, whereas 10 mutations were already described. The combined carrier frequency of hereditary hyperekplexia for the encountered founder mutations in the Saudi population was 10.9 per 10,000, which translated to a minimum disease burden of 13 patients per 1,000,000.


## Table 1. Characteristics of patients with hyperekplexia caused by *SLC6A5* variant

| | Patient 1 | Patient 2 | Patient 3 | Patient 4 | Patient 5 | Patient 6 | Patient 7 | Patient 8 | Patient 9 | Patient 10 | Patient 11 | Patient 12 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| SLC6A5 variants | Homozygous c.1969+4A>T Splice effect | Homozygous c.1969+4A>T Splice effect | Homozygous c.1346G > A missense | Homozygous c.945G>C missense | Homozygous c.945G>C missense | Homozygous c.1969+4A>T Splice effect | Homozygous c.2076_2077insAA Frameshift | Homozygous c.1738-8G>A splice effect | Homozygous c.2075_2076insAA (p.Leu693Thrfs*12) Frameshift | Homozygous c.2076_2077insAA p.(Leu693Asnfs*12) Frameshift | Homozygous c.2076_2077insAA frameshift | Homozygous c.1738-8G>A splice effect |
| Age of onset | Day 1 of life | Day 1 of life | Day 1 of life | Day 1 of life | Day 1 of life | Day 1 of life | Day 10 of life | Day 1 of life | Day 1 of life | Day 1 of life | Day 7 of life | Day 1 of life |
| Age of diagnosis | 7 months | 7 months | 2 weeks | 9 months | 9 months | 5 years | 3 years | 1 month | 11 years | 1 month | 1 month | 2 months |
| Clinical features | Excessive startle response, tonic apneic spells | Excessive startle response, tonic apneic spells | Excessive startle response, tonic apneic spells | Excessive startle, | Excessive startle response tonic apneic spells | Excessive startle response | Excessive startle response, tonic apneic spells | Excessive startle | Excessive startle response | Excessive startle response | tonic apneic spells | Excessive startle response tonic apneic spells |
| Other symptoms | Epilepsy* | None | None | None | Feeding difficulties | Strabismus Feeding difficulties Failure to thrive | Feeding difficulties | None | None | None | Generalized Epilepsy Feeding difficulties Failure to thrive | None |
| MRI Finding | thin corpus callosum | Normal | Normal | Normal | Normal | Not done | Normal | Normal | Normal | Not done | Normal | Normal |
| EEG | Multifocal discharges bilaterally | Normal | Normal | Normal | Normal | Not done | Normal | Normal | Normal | Normal | Multifocal discharges | Normal |
| Response to clonazepam | Yes | Yes | Yes | Yes (failure to respond to phenobarbital) | Yes (failure to respond to phenobarbital | Yes (failure to respond to Phenobarbital | No (failure to respond to clonazepam and levetiracetam) Response to valproate | Yes | Yes | Yes | Yes | Yes |
| Outcome | Mild intellectual disability Speech delay Hyperactivity and poor concentration | Mild intellectual disability Speech delay Hyperactivity and poor concentration | Global developmental delay | Learning difficulties | Hyperactivity | Motor delay | Normal | Normal | Mild speech delay | Normal | Mild speech delay | Normal |

## Table 2. Characteristics of patients with hyperekplexia caused by *GLRB* variant

| | Patient 1 | Patient 2 | Patient 3 | Patient 4 | Patient 5 | Patient 6 | Patient 7 |
|---|---|---|---|---|---|---|---|
| GLRB variants | Homozygous, c.583C>T p.(Gln195*) nonsense | Homozygous c.583C>T p.(Gln195*) nonsense | Homozygous c.1429G>C p.(Ala477Pro) missense | Homozygous c.583C>T p.(Gln195*) nonsense | Homozygous c.583C>T p.(Gln195*) nonsense | Homozygous c.583C>T p.(Gln195*) nonsense | Homozygous c.583C>T p.(Gln195*) nonsense |
| Age of onset | Day 1 of life | Day 1 of life | Day 1 of life | 4 years | Day 1 of life | Day 1 of life | Day 1 of life |
| Age of diagnosis | 2 months | 2 months | 17 months | 6 years | 3 years | 1 year | 1 month |
| Clinical features | Excessive startle, Tonic apneic spells | Excessive startle response, Tonic apneic spells | Excessive startle response | Excessive startle response | Excessive startle response | Excessive startle response | Excessive startle response, Tonic apneic spells |
| Other symptoms | Umbilical hernia | Feeding difficulties | Laryngomalacia | Epilepsy Hypermetropia with astigmatism | None | None | None |
| MRI Finding | Normal | Reduced myelination in the parietooccipital region | Normal | Normal | Not done | Mild atrophic changes in frontal area | Normal |
| EEG | Normal | Normal | Normal | Sharp wave discharges in the right central region | Not done | Normal | Normal |
| Response to clonazepam | Yes | Yes | Yes | Yes | Yes | Yes | Yes |
| Outcome | Mild speech delay | Normal | Mild speech delay Attending regular school | Moderate intellectual disability | Mild intellectual disability | Moderate intellectual disability | Significant speech delay. |

## Table 3. Characteristics of patients with hyperekplexia caused by *GLRA1* variant

| | Patient 2 | Patient 1 | Patient 3 |
|---|---|---|---|
| GLRA1 varient | Homozygous c.839G>A p.(Arg280His) | Homozygous c.839G>A p.(Arg280His) | Homozygous c.839G>A p.(Arg280His) |
| Age of onset | Day 1 of life | Day 1 of life | Day 1 of life |
| Age of Diagnosis | 5 months | 2 months | 2 months |
| Clinical features | Excessive startle response | Excessive startle response, Tonic apneic spells | Excessive startle response, Tonic apneic spells |
| Other symptoms | None | None | None |
| MRI Findings | Normal | Normal | Normal |
| EEG | Normal | Normal | Normal |
| Response to clonazepam | Yes | Yes | Yes |
| Outcome | Normal | Normal | Normal |

## ❖ Discussion

- The estimated carrier frequency of hereditary hyperekplexia in the Saudi population is 10.9 per 10,000.

The exact incidence of this disorder in the general population is unknown, with an estimated prevalence of <1/1000000. So far, more than 150 individuals worldwide have been reported in the literature.

- The second point of interest of this study is mode of inheritance. All patients in this study had autosomal recessive inheritance, compared to autosomal dominant in the literature.
- The third point of interest is the decreased prevalence of *GLRA1* variants in Saudi Arabia. This is the most common cause of hereditary hyperekplexia, reported in 60-65% of all cases of hyperekplexia, and was only observed in 2 (10%) patients from Saudi Arabia. SLC6A5, which encodes a pre-synaptic protein, was the most frequently identified variant in most cases of hyperekplexia examined in this study.

## ❖ conclusion

Only few studies have been published on this disorder in populations with high rates of consanguinity. This study highlights the clinical and genetic data of Saudi Arabian patients with hereditary hyperekplexia and identifies several differences from patients with hyperekplexia in Western countries.

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## REFERANCES


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