Abstract ID: - 36

Abstract Topic: - Clinical Genetics

Abstract Title: - Clinical, radiological, and genetic characterization of childhood-onset Leukodystrophies using targeted next-generation sequencing: A cost-efficient approach in resource-poor settings

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Aims: - To study the clinical, radiological and genetic features of childhood-onset Leukodystrophies by in-house genetic testing using a targeted genetic panel.

Methods: - All children with a clinico-radiological suspicion of leukodystrophy were evaluated by an in-house Ion Torrent next-generation sequencing technology. A custom gene panel was designed with the most common causes of leukodystrophies in the given setting. Genes included in the panel were GFAP, ASPA, EIF2B1-B5, GALC, L2HGDH, DARS2, EARS2, MLC1, HEPACAM, ARSA, PSAP, SUMF1, PLP1, GJC2, RNASET2, ALDH3A2, POLR3A, POLR3B and ABCD1.

Results: - Twenty two children with suspected leukodystrophies were tested by our in-house panel. Of these, 14 patients (63%) were genetically confirmed. The most common diagnoses were: X-ALD 42.85% (n=6), Vanishing-white-matter disease 21.42% (n=3), L-2-hydroxyglutaric aciduria 14.28% (n=2), Metachromatic leukodystrophy 7.14% (n=1), Alexander disease 7.14% (n=1) and POL-III related leukodystrophy 7.14% (n=1). The pathogenic variations were detected in ABCD1, EIF2B5, GFAP, L2HGDH, ARSA and POLR3A genes respectively. Majority of cases were males 71.42% (n=10/14). The mean age at presentation was 7.8 years (range 0.3-15 years). The common clinical features were developmental delay (100%), increased tone (60%), gait impairment (50%) and seizure (40%). Magnetic resonance imaging showed characteristic bilateral symmetrical white matter involvement in all children.

Conclusions: - The advent of next generation sequencing has helped in the early genetic confirmation and prenatal counselling for these disorders. Use of in-house targeted genetic panels helps in significant cost reduction and feasibility for the patients in resource-poor settings.

Keywords: - Twenty two children with suspected leukodystrophies were tested by our in-house panel. Of these, 14 patients (63%) were genetically confirmed. The most common diagnoses were: X-ALD 42.85% (n=6), Vanishing-white-matter disease 21.42% (n=3), L-2-hydroxyglutaric aciduria 14.28% (n=2), Metachromatic leukodystrophy 7.14% (n=1), Alexander disease 7.14% (n=1) and POL-III related leukodystrophy 7.14% (n=1). The pathogenic variations were detected in ABCD1, EIF2B5, GFAP, L2HGDH, ARSA and POLR3A genes respectively. Majority of cases were males 71.42% (n=10/14). The mean age at presentation was 7.8 years (range 0.3-15 years). The common clinical features were developmental delay (100%), increased tone (60%), gait impairment (50%) and seizure (40%). Magnetic resonance imaging showed characteristic bilateral symmetrical white matter involvement in all children.