Whole Genome Sequencing as a Screening Tool in Healthy Population: Lesson learned from 110 cases

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BACKGROUND

- Whole genome sequencing (WGS) has been widely considered a powerful tool in identification of disease- causing variants to ascertain clinical diagnoses.
- With WGS's uniformed coverage for both exonic and intronic regions, the expected clinical sensitivity of WGS is up to 40-50%.
- the utilization of WGS as a screening test for healthy individuals has increased.
- PKI healthy WGS includes copy number variation analysis and mitochondrial DNA analysis.
- We have performed 110 WGS on reportedly healthy asymptomatic individuals

RESULTS

Figure 1: Healthy WGS overall yield

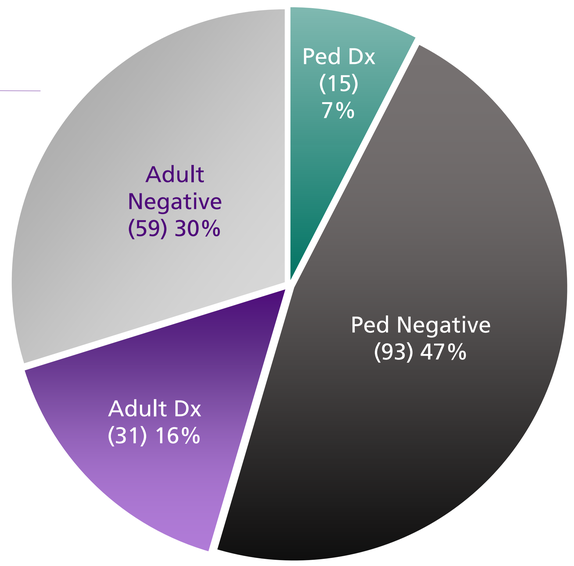

Figure 2: Type of variants in Pediatric and Adult Dx Findings

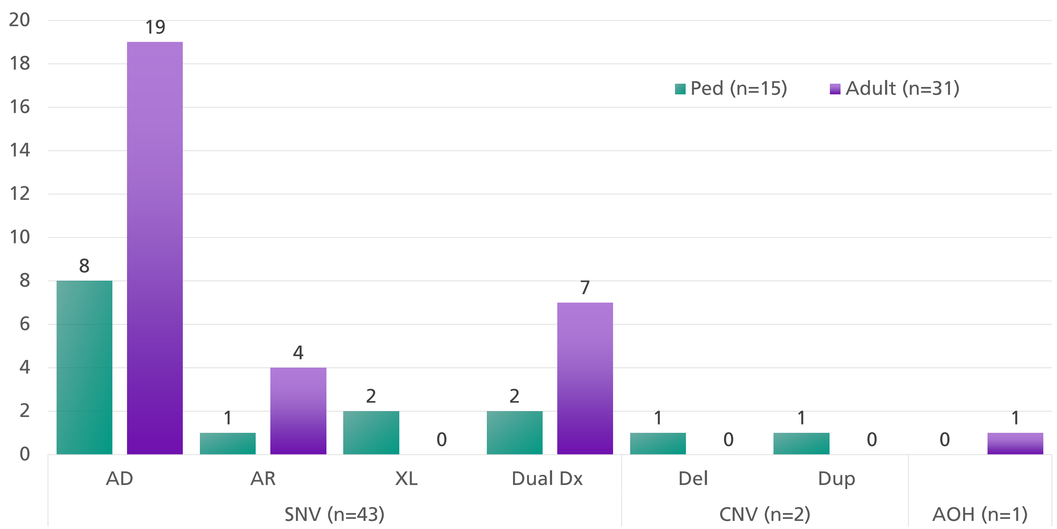

Figure 3: Associated Diseases in Pediatric and Adult Cohort

Category	# of genes	Genes	# of cases
Hereditary cancer syndrome	7	*SDHA, MITF, CHEK2, RAD50, FH, APC, PTEN*	12
Neurodegeneration	2	*APOE, LRRK2*	11
Neurology	2	*PRRT2, MME*	2
Endocrinology	3	*ABCC8, PROKR2, NOBOX*	3
Skeletal dysplasia	2	*ARSE, FGFR3*	2
Biochemical	3	*HFE, GALT, G6PD*	7
Pulmonary	2	*SFTPC, SMAD9*	2
Urology	2	*SLC34A1, SLC3A1*	2
Cardiovascular	3	*MFAP5, MYBPC3, PRKAG2*	4
Muscular	2	*AMPD1, SCN4A*	3
Other (deafness, skin, dysmorphism, fever)	4	*IRF6, FLG, TECTA, MEFV*	4

MULTIPLE DIAGNOSES EXAMPLES

Case/Age	Dx findings 1	Associated disease	Dx findings 2	Associated disease
1/PED	*AMPD1*, c.[133C>T;242C>T] (p.[Gln45Ter; Pro81Leu]), Pathogenic with reduced penetrance, homozygous	Myopathy due to myoadenylate deaminase deficiency	*SDHA*, c.1534C>T (p.Arg512Ter), Likely Pathogenic	Paragangliomas 5
2/PED	*HFE*, c.187C>G (p.His63Asp); c.845G>A (p.Cys282Tyr), Pathogenic with reduced penetrance	Hemochromatosis	*TECTA*, c.2342_2345dup, Pathogenic	Deafness, autosomal dominant 8/12
3/ADULT	*LRRK2*, c.6055G>A(p.Gly2019Ser), Pathogenic	Parkinson disease	*APOE*, c.388T>C (p.Cys130Arg), risk factor	Alzheimer disease
4/ADULT	*MYBPC3*, c.3697C>T (p.Gln1233Ter), Pathogenic.	Hypertrophic cardiomyopathy; Dilated cardiomyopathy; Left ventricular noncompaction 10	*SLC3A1*, c.1354C>T (p.Arg452Trp), Pathogenic	Cystinuria
4/ADULT	*MME*, c.467del, Pathogenic	Charcot-Marie-Tooth disease, axonal, type 2T; Spinocerebellar ataxia 43	*PROKR2*, c.254G>A (p.Arg85His), Pathogenic	Hypogonadotropic hypogonadism 3 with or without anosmia
5/ADULT	*APC*, c.3920T>A (p.Ile1307Lys), Risk Factor.	Familial adenomatous polyposis (FAP)	*G6PD*, c.563C>T (p.Ser188Phe), Pathogenic, Hemizygous	Hemolytic anemia, G6PD deficient (favism)
6/ADULT	*MYBPC3*, c.3190+5G>MYBPC3 A, Pathogenic	Hypertrophic cardiomyopathy; Dilated cardiomyopathy; Left ventricular noncompaction 10	*NOBOX*, c.1295_1310delinsGAG, Likely Pathogenic	Premature ovarian failure 5
7/ADULT	*PTEN* c.801+1del, Pathogenic	Cowden syndrome 1; Macrocephaly/autism syndrome; Lhermitte-Duclos syndrome	*PRKAG2* c.905G>A(p.Arg302Gln), Pathogenic	Cardiomyopathy, hypertrophic 6; Glycogen storage disease of heart, lethal congenital; Wolff-Parkinson-White syndrome
8/ADULT	*MITF*, c.952G>A (p.Glu318Lys), Pathogenic	Melanoma, cutaneous malignant, susceptibility to, 8	*APOE*, c.388T>C (p.Cys130Arg), risk factor	Alzheimer disease

CONCLUSION

- Healthy WGS screening test can be considered as a new standard of care along with newborn screening and carrier screening.
- Healthy WGS allows individuals to learn their risk for medically actionable conditions and carrier status prior to family planning
- Healthy WGS provide valuable information for the healthcare providers to help their patients making suitable prophylactic plans, finding medical management guidelines, selecting optimal dosage of medications and adapting to a healthy life style.