Whole Genome Analysis of 342 adult cases of Obesity and related metabolic disorders in highly consanguineous population: A Saudi Genome Study

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Background

Recent advantages for direct sequencing of whole genomes or exomes offers the most comprehensive approach for the detection of rare sequence variants with large effects. Coupled with information about human disease and other traits, an unparalleled opportunity currently exists to identify rare coding variants within genes that cause disease. Metabolic disorders like Obesity, Polycystic and type-2-diabetes (T2D) represent a worldwide epidemic that impose an enormous burden on public health. The Saudi population with one of the highest rate of consanguineous unions and high prevalence of both obesity and or T2D is ideal for identification, through whole-genome sequencing, of homozygous mutations with large effect on obesity and T2D.

objective

- To screen and identify sequence variants that associate with obesity, polycystic and type 2 diabetes (T2D) by WES technology
- Identifying rare variants unique to Saudi population
- This study will aid in developing novel therapeutic approaches for this difficult-to-treat metabolic disorders

Methods

- Patients recruited: Saudi, average body mass index ~37.5,averae Age ~ 45
- Whole genome sequencing was done on total 342 patients using Novaseq® platform
- Rare/ Homozygous LOF/missense were detected at MAF < 1% while Heterozygous LOF/missense were detected at MAF < 0.02%

Results

- Most samples show detectable inbreeding as expected.
- Average number of homozygous loss-of-function mutations per case is 0.9-1.2.
- Multiple known/expected pathogenic mutations identified in genes like ***ABCC2, UPB1, HRG, FLT4, MSH3,TRAPPC2,CD36, CEL*** and other.
- Likely pathogenic variants include: ***PLIN1, LIPE, PAX4***.
- Homozygous/Hemizygous loss-of-function (LOF: essential splice, frameshift, stop gained) also reported as "Private" for our cohort in multiple novel genes (not in OMIM) like: ***WDR54, ASB12, USP26, CTAG2, ZXDA***, and others.

Known Pathogenic mutations identified in our Saudi Cohort

Gene	Mutation	OMIM disease (MOI)
ABCC2	NM_000392.4:c.1031+2T>C	Dubin-Johnson syndrome (AR)
UPB1	NM_016327.2:c.105-2A>G	Beta-ureidopropionase deficiency (AR)
HRG	NP_000403.1:p.Gly191GlufsTer36	Thrombophilia (AD)
FLT4	NM_002020.4:c.3220-35_3220-2delTCCACCACGGGACAAGCTTCCCTCTGTCTCCCCA,NM_182925.4:c.3220-35_3220-2delTCCACCACGGGACAAGCTTCCCTCTGTCTCCCCA	Lymphatic malformation (AD)
MSH3	NP_002430.3:p.Ala60ProfsTer23	Familial adenomatous polyposis (AR)
MSH3	NP_002430.3:p.Ala61ProfsTer25	Familial adenomatous polyposis (AR)
TRAPPC2	NP_001122307.2:p.Trp4Ter	Spondyloepiphyseal dysplasia tarda (XLR)
CEL	NM_001807.4:c.346C>T NP_001798.2:p.Gln116Ter	Maturity-onset diabetes of the young, type VIII (AD)

Likely Pathogenic mutations identified in our Saudi Cohort

Gene	Mutation	OMIM disease (MOI)
PLIN1	NM_002666.5:c.1210-1G>T	Lipodystrophy, familial partial, type 4 (AD)
LIPE	NM_005357.4:c.280G>A p.Ala94Thr	Lipodystrophy, familial partial, type 6 (AR)
HNF1B	NM_000458.4:c.1006C>T p.His336Tyr	Diabetes mellitus, noninsulin-dependent (AD)
MPL	NM_005373.2:c.317C>T p.Pro106Leu	Thrombocythemia (AD/AR)
PAX4	NM_001366110.1:c.421C>T p.Arg141Trp	Diabetes mellitus, ketosis-prone, susceptibility to (AD,AR)

Selected Unique "Private" Hemi/Homozygous LOF mutations

Gene	Mutation
WDR54	NP_001307752.1:p.Gln71Ter, NP_001307753.1:p.Gln56Ter
ASB12	NP_569059.3:p.Gln283ArgfsTer4
USP26	NP_114113.1:p.Gly488TrpfsTer6
MUC19	NP_775871.2:p.Leu5593ThrfsTer134
CTAG2	NP_066274.2:p.Glu189Ter
ZXDA	NP_009087.1:p.Gln138Ter

Conclusion

- The Saudi population is one of the highest rate of consanguineous unions and high prevalence of obesity and other related metabolic disorders.
- By analyzing whole-genome data from Saudis with obesity and/or T2D/ PCOS, we found some known Pathogenic / likely pathogenic mutations reported before identified in our cohort
- Rare Homozygous / Hemizygous LOF mutations (coding and splicing variants) MAF <1% were identified in our Saudi cohort not reported before
- Our data will provide insight into the pathophysiology of these conditions and potentially new targets for therapeutic developments.
- Future analysis for larger cases and control sets is required to perform a GWAS study