**Table 1.** Diagnostic yield in selected cerebellar ataxia families in three groups

|  |  |
| --- | --- |
|  | **Number of families** |
|  | **ADCA** | **SPEOCA** | **SPLOCA** |
| ***Total families in this study, N=50*** | ***14*** | ***22*** | ***14*** |
| **S-WES, N=50 families** | **14** | **22** | **14** |
| **Defined genetic etiology , N=31 families** | 5 | 18 | 8 |
| Pathogenic +/- Likely pathogenic variant | 5 | 17 | 7 |
| Variants of uncertain significance |  | 1 | 1 |
| **Clinically relevant variant, S-WES (62%)** | **36% (5/14)** | **82%(18/22)** | **57%(8/14)** |
| **F-WES, N=7 families** | **5** | **1** | **1** |
| **Defined genetic etiology , N=4 families** | 3 | 1 |  |
| Pathogenic +/- Likely pathogenic variant | 3 |  |  |
| Variants of uncertain significance in new gene | 1 |  |
| **Clinically relevant variant, F-WES (57%)** | **60%(N=3)** | **100%(N=1)** |  |
| **Overall clinically relevant variant,****70% (35/50) families** | **57% (8/14)** | **86% (19/22)** | **57% (8/14)** |
|
| ***Genetically characterised families with,*** |  |  |  |
| Definitive diagnosis, 50% | 6 | 14 | 5 |
| Probable diagnosis, 14% | 2 | 3 | 2 |
| VUS and New gene, 6% |  | 2 | 1 |

 WES-Whole exome sequencing, S-singleton, F-family based design, VUS- variants of uncertain significance

**Table 2.** Details of identified clinically relevant variants

|  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **S.N.** | **Patient ID** | **Gender-Age (onset)** | **Group** | **Gene** | **Phenotype (OMIM)** | **Disease model (variant state)** | **HGVS ID** | **Variant Type** | **Variant status** | **HGMD**  | **ClinVar** | **Variant class (ACMG)** |
| **25 families with definitive diagnostic with pathogenic and/ or likely pathogenic variants** |
| ***Variants in known genes of SCA***  |
| 1 | AT1682 | M-54 (53.5) | ADCA | *AFG3L2* | SCA28, 610246, AD | AD (Het) | NM\_006796.3:c.2173A>G:p.Lys725Glu | Missense | Rare | Absent | Absent | Likely Pathogenic |
| 2 | AT2521 | F-42 (35) | ADCA | *TTBK2* | SCA11, 604432, AD | AD (Het) | NM\_173500.4:c.1304\_1305GA:p.Asp436fs | Frameshift | Reported | CD104909 | Pathogenic | Pathogenic |
| 3 | AT2221 | M-17 (15) | ADCA | *FAT2* | SCA45,617769, AD | AD (Het) | NM\_001447.2:c.6779T>A:p.Val2260Asp | Missense | Novel | Absent | Absent | Likely Pathogenic |
| 4 | AT2832 | F-55 (43) | ADCA | *MME* | SCA43, 617018 , AD | AD (Het) | NM\_000902.4:c.1121G>A:p.Arg374Lys | Missense | Rare | Absent | Absent | Likely Pathogenic |
| 5 | AT2166 | M-40 (29) | SPEOCA | *TMEM240* | SCA21, 607454, AD | AD (Het) | NM\_001114748.2:c.509C>T:p.Pro170Leu | Missense | Reported | Absent | Pathogenic | Pathogenic |
| 6 | AT2705 | F-18 (12) | SPEOCA | *GRM1* | SCA44, 617691, AD | AD (Het) | NM\_001278064.1:c.2603G>C:p.Arg868Pro | Missense | Rare | Absent | Absent | Likely Pathogenic |
| 7 | AT2176 | F-26 (24) | SPEOCA | *FAT1* | SCA, N.A., AD | AD (Het) | NM\_005245.4:c.2621C>T:p.Thr874Met | Missense | Rare | Absent | Absent | Likely pathogenic |
| 8 | AT1798 | M-55 (53.5) | SPLOCA | *EEF2* | SCA26, 609306, AD | AD (Het) | NM\_001961.4:c.159G>C:p.53Glu53Asp | Missense | Novel | Absent | Absent | Likely pathogenic |
| 9 | AT1889 | M-49 (44) | SPLOCA | *ELOVL5* | SCA38, 615957, AD | AD (Het) | NM\_021814.5:c.689G>T:p.Gly230Val | Missense | Reported | Absent | Pathogenic | Pathogenic |
| 10 | AT2216 | M-71 (57) | SPLOCA | *KCNC3* | SCA13, 605259, AD | AD (Het) | NM\_004977.2:c.1196C>T:p.Ser399Leu | Missense | Rare | Absent | Absent | Likely Pathogenic |
| 11 | AT1864 | F-68 (66.5) | SPLOCA | *SPTBN2* | SCA5, 600224, AD | AD (Het) | NM\_006946.4:c.1337G>A:p.Arg446His | Missense | Rare | Absent | Absent | Likely Pathogenic |
| 12 | AT2137 | M-38 (31) | ADCA | *SETX* | SCAR1, 606002, AR;ALS4,602433, AD | AD (Het) | NM\_015046.7:c.5278G>A:p.Ala1760Thr | Missense | Reported | Absent | VUS | Likely pathogenic |
| ***Variants in known genes of SCAR*** |
| 13 | AT2880 | F-12 (10) | SPEOCA | *ATM* | AT, 208900 , AR | AR (CHet) | NM\_000051.4:c.7307G>A:p.Arg2436Lys | Missense | Reported | Absent | VUS | Pathogenic |
| NM\_000051.4:c.5631\_5635delinsA:p.Phe1877LeufsTer | Frameshift | Reported | Absent | Pathogenic | Pathogenic |
| 14 | AT2278 | F-30 (4) | SPEOCA | *SACS* | ARSACS, 270550 , AR | AR (Hmz) | NM\_014363.6:c.429\_430del:p.Trp144Valfs | Frameshift | Rare | Absent | Absent | Pathogenic |
| 15 | AT1018 | F-31 (20) | SPEOCA | *SETX* | SCAR1, 606002, AR | AR (CHet) | NM\_015046.7:c.6859C>T:p.Arg2287Ter | Nonsense | Reported | CM111221 | Absent | Pathogenic |
| NM\_015046.7:c.2623\_2626del:p.Val875Phefs | Frameshift | Rare | Absent | Absent | Pathogenic |
| 16 | AT1554 | M-28 (16) | SPEOCA | AR (CHet) | NM\_015046.7:c.5927T>G:p.Leu1976Arg | Missense | Reported | CM050777 | Pathogenic | Pathogenic |
| NM\_015046.7:c.971A>G:p.Tyr324Cys | Missense | Novel | Absent | Absent | Likely pathogenic |
| 17 | AT2807 | M-16 (8) | SPEOCA | AR (CHet) | NM\_015046.7:c.7117A>G:p.Thr2373Ala | Missense | Novel | CM087873, T>G reported | Absent | Likely pathogenic |
| NM\_015046.7:c.6473G>A:p.Gly2158Ala | Missense | Novel | Absent | Absent | Likely pathogenic |
| ***Variants in HSP and other neurological disorders genes in AR inheritance*** |
| 18 | AT1796 | M-39 (28) | ADCA | *CAPN1* | SPG76, 616907, AR | AR (Hmz) | NM\_005186.4:c.658G>A:p.Gly220Arg | Missense | Rare | Absent | Absent | Likely pathogenic |
| 19 | AT1756 | M-46 (43) | SPLOCA | *SPG7* | SPG7, 607259, AR | AR (CHet) | NM\_003119.4:c.1061G>C:p.Gly354Ala | Missense | Reported | CM131104 | Absent | Pathogenic |
| NM\_003119.4:c.233T>A:p.Leu78Ter | Nonsense | Reported | CM081826 | Pathogenic | Pathogenic |
| 20 | AT1941 | M-36 (16) | SPEOCA | AR (Hmz) | NM\_003119.4:c.233T>A:p.Leu78Ter | Nonsense | Reported | CM081826 | Pathogenic | Pathogenic |
| 21 | AT2037 | M-38 (24) | SPEOCA | *GBA2* | SPG46, 614409 , AR | AR (Hmz) | NM\_020944.3:c.2479G>A:p.Gly827Arg | Missense | Rare | Absent | Absent | Likely pathogenic |
| 22 | AT2028 | F-19 (11) | SPEOCA | *CEP290* | 610188, AR | AR (Hmz) | NM\_025114.4:c.4910T>C:p.Leu1637Pro | Missense | Rare | Absent | Absent | Likely pathogenic |
| 23 | AT1876 | M-26 (24) | SPEOCA | *GPR88* | 616939, AR | AR (Hmz) | NM\_022049.3:c.243C>G:p.Cys81Trp | Missense | Novel | Absent | Absent | Likely pathogenic |
| 24 | AT2808 | M-19 (6) | SPEOCA | *NPC1* | 257220 , 257220, AR | AR (Hmz) | NM\_000271.5:c.2068A>T:p.Ile690Phe | Missense | Novel | Absent | Absent | Likely pathogenic |
| 25 | AT2560 | F-14 (8) | SPEOCA | *RELN* | 257320, AR | AR (Hmz) | NM\_005045.4:c.5827G>C:p.Asp1943His | Missense | Rare | Absent | Absent | Likely pathogenic |
| **Seven families with probable diagnostic pathogenic/likely pathogenic variants** |
| 26 | AT2910 | M-22 (18) | ADCA | *SLC2A1* | 606777, AD/AR | AR (CHet) | NM\_006516.3:c.1438G>A:p.Glu480Lys | Missense | Reported | Absent | VUS | Likely Pathogenic |
| NM\_006516.3:c.616T>C:p.Phe206Leu | Missense | Rare | Absent | Absent | Likely Pathogenic |
| 27 | AT2029 | M-52(50.5) | SPLOCA | *FAT1* | SCA, N.A., AD | AD (Het) | NM\_005245.4:c.660G>A:p.Asp1554Asn | Missense | Rare | Absent | Absent | Likely Pathogenic |
| 28 | AT1965 | M-37(34) | ADCA | *EMC1* | 616875, AD | AD (Het) | NM\_015047.3:c.200dupA:p.Asn67LysfsTer13 | Frameshift | Novel | Absent | Absent | Pathogenic |
| 29 | AT1943 | F-43(38) | SPEOCA | *DNMT1* | 604121, AD | AD (Het) | NM\_001130823.3:c.3218A>G:p.Gln1073Arg | Missense | Novel | Absent | Absent | Likely Pathogenic |
| 30 | AT1968 | F-27(24) | SPEOCA | *PSEN1* | 607822, AD | AD (Het) | NM\_000021.4:c.568A>G:p.Asn190Asp | Missense | Rare | Absent | Absent | Likely Pathogenic |
| 31 | AT2099 | M-21 (7) | SPEOCA | *NF1* | 162200, AD | AD (Het) | NM\_001042492.2:c.2902A>G:p.Met968Val | Missense | Reported | Absent | VUS | Likely Pathogenic |
| 32 | AT2834 | M-52(51) | SPLOCA | *CTBP1* | 617915, AD | AD (Het) | NM\_001328.3:c.736C>T:p.Leu246Phe | Missense | Rare | Absent | Absent | Likely Pathogenic |
| **Three families with variants of uncertain significance** |
| ***Variants in new candidate gene*** |
| 33 | AT1929 | F-27 (23) | SPEOCA | *SPTB* | 616649, AD | AR (CHet) | NM\_001355436.2:c.1985C>T:p.Ser662Phe | Missense | Novel | Absent | Absent | VUS |
| NM\_001355436.2:c.4147C>A:p.Leu1383Met | Missense | Rare | Absent | Absent | VUS |
| ***Variants in SCA genes*** |
| 34 | AT2833 | M-53 (52) | SPLOCA | *SPTBN2* | SCA5, 600224,AD | AD (Het) | NM\_006946.4:c.5276A>G:p.Asn1759Ser | Missense | Rare | Absent | Absent | VUS |
| 35 | AT1803 | M-31(30) | SPEOCA | *KIF26B* | SCA, N.A., AD | AD (Het) | NM\_018012.4:c.4771C>T:p.Arg1591Trp | Missense | Rare | Absent | Absent | VUS |

M-Male, F-Female, SCA-spinocerebellar ataxia, AD-autosomal dominant, AR autosomal recessive, SCAR-Spinocerebellar ataxia, autosomal recessive, ARSACS- Autosomal recessive spastic ataxia of Charlevoix-Saguenay, AT- Ataxia-telangiectasia, SPG- Spastic paraplegia, Het-Heterozygous, CHet- Compound heterozygous, Hmz- Homozygous alternate, VUS- Variant of uncertain significance, rare denotes frequency <0.01%